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Peptide, Herstellung und deren Verwendung

Peptides, production et leur utilisation

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Description

The present invention relates to a new peptide, exhibiting endothelin receptor antagonistic action, which is pharmaceutically useful as a therapeutic agent for hypertension, a therapeutic agent for cerebrovascular disease, a therapeutic agent for renal disease, and a therapeutic agent for asthma; a method of production thereof and a use thereof.

Endothelin (ET), is a vasoconstricting peptide comprising 21 amino acids, isolated from swine arterial endothelial culture supernatant and structurally determined by Yanagisawa et al. [Yanagisawa et al.: Nature, Vol. 332, pp. 411-415, 1988]. Endothelin was later found to exhibit various actions, and endothelin antibodies as endothelin antagonists have proven effective in the treatment of myocardial infarction, renal failure and other diseases. Since endothelin is present in live bodies and exhibits vasoconstricting action, it is expected to be an endogenous factor involved in the regulation of the circulatory system, and may be associated with hypertension, cardiovascular diseases such as myocardial infarction, and renal diseases such as acute renal failure. Since it also exhibits bronchial smooth muscle constricting action, it may be associated with asthma.

Recently, we have known endothelin antagonists described in (1) Japanese Patent Publication Nos. 3130299/1991, (2) EP-A-457,195, (3) EP-A-460,679. As examples, the above (1), (2) and (3) describes respectively

Boc-Leu-D-Trp(For)-D-Glu(OBzl)-Ala-OPac (1),
Boc-L-Leu-D-Trp(CH_3)-D-Pya-OH (2),
Boc-Ile-D-Trp-β-Ala-OH (3).

These peptides, however, have defects which their endothelin antagonist activities are low. Then these peptide have not been used practically now.

If an excellent endothelin receptor antagonist is obtained, it will help clarify the action mechanism of endothelin, and will also offer a useful therapeutic agent for the above diseases. Accordingly, the object of the present invention is to provide a new compound having such an excellent effect.

The present inventors have studied intensively to solve the above problems. As a result, the inventors have succeeded in preparing a novel and relatively low molecular weight peptide which is different from the above (1), (2), (3) and have found that the peptide has an unexpectedly excellent receptor-antagonistic activity. According to further investigation, the inventors have attained the present invention.

Accordingly, the present invention relates to a peptide represented by the formula [I]:

$$
R_1\text{-CO-}\underset{}{\overset{R_2}{\overset{|}{N}}}\text{-}\underset{(L)}{\overset{R_3}{\overset{|}{CH}}}\text{-CO-NH-}\underset{(D)}{\overset{R_4}{\overset{|}{CH}}}\text{-CO-}\overset{R_5}{\overset{|}{N}}\text{-}\overset{R_6}{\overset{|}{CH}}\text{-}(CH_2)n\text{-CO-NH-}(CH_2)m\text{-CO-X} \quad [I]
$$

wherein R_1 represents

(i) a straight or branched C_1-C_{10} alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_3-C_8 cycloalkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_1-C_6 alkoxycarbonyl group, a C_6-C_{12} aromatic hydrocarbon group which may be substituted by a halogen atom, hydroxy group, C_1-C_3 alkoxy group or C_1-C_3 alkyl group and a 5- to 10-membered aromatic heterocyclic group,

(ii) a C_3-C_{10} cycloalkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_1-C_6 alkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group and a C_1-C_6 alkoxycarbonyl group, or the cycloalkyl group as condensed with a benzene ring,

(iii) a straight or branched C_1-C_8 alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group and a C_1-C_6 alkoxycarbonyl group,

(iv) a C_6-C_{15} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_6 alkoxycarbonyl group,

(v) a 5- to 6-membered aromatic heterocyclic group which contains 1 to 4 heteroatoms of O, S and N, or the

group as condensed with a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_6 alkoxycarbonyl group, or

(vi) a group represented by R_7NH- or R_8R_9N- wherein R_7, R_8 and R_9 independently represent (i) a C_4-C_{10} alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a hydroxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, a C_6-C_{12} aromatic hydrocarbon group which may be substituted by a halogen atom, a hydroxy group, a C_1-C_3 alkoxy group or a C_1-C_3 alkyl group, and a 5- to 10- membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, S and N, (ii) a C_5-C_{10} cycloalkyl group, which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a hydroxy group, a carboxyl group and a C_1-C_6 alkylcarbonyl group, (iii) a C_6-C_{12} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxy group, a carboxyl group and a C_1-C_6 alkylcarbonyl group, or (iv) a 5-to 10- membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, N and S or the group as condensed with a benzene ring wherein a carbon atom which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxyl group, a carboxyl group and a C_1-C_6 alkylcarbonyl group, and a nitrogen atom which may be substituted by 1 to 3 C_1-C_6 alkyl groups, and R_8 and R_9 may bind together to form a 5- to 13-membered nitrogen-containing heterocyclic ring which may have 1 or 2 hetero atoms such as an oxygen atom and a sulfur atom, the said 5- to 13-membered nitrogen-containing heterocyclic ring being optionally substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a phenyl group, a halogen atom, a nitro group, a cyano group, a hydroxy group, a C_1-C_4 alkoxy group, a C_1-C_4 alkylthio group, an amino group, a mono- or di-C_1-C_4 alkylamino group, a C_1-C_4 alkylcarbonylamino group, a C_1-C_4 alkylsulfonylamino group, a C_1-C_4 alkoxycarbonyl group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_4 alkylcarbonyloxy group and a 5- or 6-membered heterocyclic group having 1 to 4 hetero atoms such as O, S and N;

R_2 and R_5 independently represent a hydrogen atom or a straight or branched C_1-C_6 alkyl group;
R_3 is a C_1-C_8 alkyl, C_3-C_8 cycloalkyl or C_3-C_8 cycloalkyl-C_1-C_8 alkyl group wherein a methylene (-CH_2-) of the group may be interrupted by an oxygen atom or a sulfur atom;
R_4 is a heterocyclic-substituted C_1-C_6 alkyl group which may be substituted wherein the heterocycle is a 5- or 6-membered heterocyclic group having 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring, and the carbon atom of the heterocyclic-substituted C_1-C_6 alkyl group may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a hydroxyl group, a carboxyl group, a C_1-C_6 alkoxy group and a C_1-C_6 alkylcarbonyl group, and the nitrogen atom of the heterocyclic-substituted C_1-C_6 alkyl group may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkylcarbonyl group and a hydroxy-C_1-C_6 alkyl group;
R_6 represents a hydrogen atom, a straight or branched C_1-C_6 alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of (i) a C_6-C_{15} aromatic hydrocarbon group, (ii) a 5- to 6-membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, S and N or the group as condensed with another aromatic ring, (iii) a sulfur-containing group selected from the group consisting of a thione, mercapto, methylthio, ethylthio and phenylthio, (iv) a oxygen-containing group selected from the group consisting of a ketone, hydroxy, methoxy, ethoxy, phenoxy and benzyloxy group and (v) a nitrogen-containing group selected from the group consisting of an amino, N-methylamino, N-ethylamino and guanidino, a C_6-C_{12} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylcarbonyl group and a C_1-C_6 alkoxycarbonyl group, or a 5- or 6-membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylcarbonyl group and a C_1-C_6 alkoxycarbonyl group;
X is (i) a group resulting from elimination of one hydrogen atom from the α-amino group an an α-amino acid having an aromatic cyclic group or (ii) an alkylamino group substituted by an aromatic cyclic group wherein the aromatic cyclic group is (i) a C_6-C_{15} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group and a C_1-C_6 alkoxycarbonyl group, or (ii) a 5- or 6-membered aromatic heterocyclic group having 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_6 alkoxycarbonyl group,

n represents 0 or an integer of 1 to 4 and

m represents an integer of 2 to 6,

or a salt thereof, a method of production thereof and a pharmaceutical composition containing peptid [I] or a pharmacologically acceptable salt thereof.

Throughout in the specification, the compound [I] or peptide [I] may include the compound or peptide itself and the salt thereof.

Abbreviations for amino acids, peptides and others used in the present specification are based on abbreviations specified by the IUPAC-IUB Commission on Biochemical Nomenclature or abbreviations in common use in relevant fields. Some examples are given below.

Ala	: Alanine
Gly	: Glycine
Val	: Valine
Nva	: Norvaline
Leu	: Leucine
Ile	: Isoleucine
Nle	: Norleucine
Met	: Methionine
Trp	: Tryptophan
Tyr	: Tyrosine
Phe	: Phenylalanine
Glu	: Glutamic acid
Asp	: Aspartic acid
Gln	: Glutamine
Asn	: Asparagine
His	: Histidine
Cys	: Cysteine
Cha	: Cyclohexylalanine
Phg	: Phenylglycine
βAla	: β-Alanine (β-Aminopropionic acid)
GABA	: γ-aminobutyric acid
Aib	: 2-aminoisobutyric acid
εAhx	: ε-aminocaproic acid
(m-F)Tyr	: m-fluorotyrosine
(p-F)Phe	: p-fluorophenylalanine
Trp(Me)	: N^{in}-methyltryptophan
Trp(CH_2OH)	: N^{in}-hydroxymethyltryptophan
Trp(CHO)	: N^{in}-formyltryptophan
Pya(2)	: 2-pyridylalanine
Pya(3)	: 3-pyridylalanine
(I)Tyr	: 3-Iodo-tyrosine
Thg(2)	: 2-thienyl-glycine
Thg(3)	: 3-thienyl-glycine
Thi	: 2-thienyl-alanine

The substituents, protective groups and reagents often used in the present specification and claims are symbolized as follows:

Ph	:Phenyl
Boc	:tert-butoxycarbonyl
Bzl	:Benzyl
HONB	:N-hydroxy-5-norbornene-2,3-dicarboxyimide
DCC	:N,N'-dicyclohexylcarbodiimide
DCHA	:N,N'-dicyclohexylamine
WSCD	:1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
HOBt	:N-hydroxybenzotriazole
TosOH	:p-toluenesulfonic acid

OPac	:Phenacyl ester
Ind	:1-carboxyindan-2-yl
Iqu	:3-carboxy-1,2,3,4-tetrahydroisoquinolin-2-yl
Dba	:10,11-dihydro-5H-dibenz(b,f)azepin-5-yl
Pym	:Pyrimidyl
Pip	:Piperazyl

For example, in the present specification, Glu-OBzl represents a benzyl ester at the 1-carboxyl group of Glu; Glu(OBzl) represents a benzyl ester at the 5-carboxyl group of Glu; Asp-$NHCH_2CH_3$ represents an ethylamide at the 1-carboxyl group of Asp; Asp($NHCH_2CH_3$) represents an ethylamide at the 4-carboxyl group of Asp.

With respect to the above formula [I], R_1 represents an oil-soluble group. The oil-soluble group may be an alkyl group, cycloalkyl group, alkoxy group, aromatic cyclic group and amino group having a substituent, which groups may be further substituted, as follows.

The alkyl group for R_1 is a straight or branched alkyl group having 1 to 10 carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl. Lower alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl, n-hexyl) are particularly preferable.

These alkyl groups may be substituted by 1 to 3 substituents. Example substituents include C_{3-8} cycloalkyls (e.g., cyclopentyl, cyclohexyl), halogens (e.g., fluorine, chlorine, bromine, iodine), C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy), C_{1-6} alkylthios (e.g., methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, tert-butylthio), C_{1-6} alkoxycarbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl), aromatic cyclic groups (e.g., C_{6-12} aromatic hydrocarbon groups which may be substituted by a halogen, hydroxy, C_{1-3} alkoxy, C_{1-3} alkyl group, such as phenyl, fluorophenyl, chlorophenyl, bromophenyl, hydroxyphenyl, methoxyphenyl, methylphenyl, 1-naphthyl and 2-naphthyl, and 5- to 10- membered aromatic heterocyclic groups which contain 1 to 4 hetero atoms such as O, S, N and others such as furyl, thienyl, thiazolyl, indolyl, pyridyl, pyranyl, imidazolyl, pyrimidyl and quinolyl). The number of substituents of these alkyl groups is preferably 1 to 3.

The cycloalkyl group for R_1 is a cycloalkyl group having 3 to 10 carbon atoms, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, bornyl and norbornyl. These cycloalkyl groups may be substituted by 1 to 3 substituents. Example substituents include C_{1-6} alkyls (e.g., methyl, ethyl, n-propyl, n-butyl), halogens (e.g., fluorine, chlorine, bromine, iodine), C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy), C_{1-6} alkylthios (e.g., methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, tert-butylthio) and C_{1-6} alkoxycarbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl). The number of substituents of these cycloalkyl groups is preferably 1 to 3. These cycloalkyl groups as condensed with another ring such as a benzene ring (e.g., indan-1-yl, indan-2-yl, 1,2,3,4-tetrahydronaphthalene-1-yl, 1,2,3,4-tetrahydronaphthalene-2-yl) are also included.

The alkoxy group for R_1 is a straight or branched alkoxy group having 1 to 8 carbon atoms, including methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentyloxy, isoamyloxy, tert-amyloxy, neopentyloxy, n-hexyloxy, n-heptyloxy and n-octyloxy. These alkoxy groups may be substituted by 1 to 3 substituents. Example substituents include C_{3-8} cycloalkyl groups (e.g., cyclopentyl, cyclohexyl), C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy) and C_{1-6} alkoxycarbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl). The number of substituents of these alkoxy groups is 1 to 3. The alkyl group or alkoxy group for R_1 is preferably branched rather than straight.

The aromatic cyclic group for R_1 may be an aromatic hydrocarbon group or an aromatic heterocyclic group. The aromatic hydrocarbon group has 6 to 15 carbon atoms such as phenyl, α-naphtyl. These aromatic hydrocarbon groups may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms (ex. fluorine, chlorine, bromine), hydroxy group, C_{1-6} alkyl group (ex. methyl, ethyl), C_{1-6} alkoxy group (ex. methoxy, ethoxy), carboxyl group, C_{1-6} alkylcarbonyl (ex. formyl, acetyl), C_{1-6} alkoxy carbonyl (ex. methoxycarbonyl). Examples of aromatic hydrocarbon groups which may be substituted are preferably phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methylphenyl, 1-naphthyl, 2-naphthyl. The aromatic heterocyclic groups are 5- or 6-membered groups having 1 to 4 hetero atoms of O, S, and N (e.g., 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, thiazol-4-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyranyl) and these groups as condensed with other aromatic rings such as a benzene ring (e.g., indol-3-yl, N-methylindol-3-yl, 2-quinolyl, quinoxalin-2-yl). These aromatic heterocyclic groups may have 1 to 3 substituents which are same as those of the above mentioned aromatic hydrocarbon groups.

The amino group substituted for R_1 is a mono-substituted amino group (R_7NH-) or a di-substituted amino group (R_8R_9N-), wherein R_7, R_8 and R_9 independently represent groups capable of providing oil solubility for the substituted amino group. Examples of such groups for R_7, R_8 and R_9 include alkyl groups having 4 to 10 carbon atoms and, cycloakyl groups or aromatic cyclic groups having 5 to 10 carbon atoms. The alkyl group having 4 to 10 carbon atoms, includes n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl

and n-decyl. The cycloalkyl group has 5 to 10 carbon atoms, including cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, bornyl and norbornyl. Exampl aromatic cyclic groups for R_7, R_8 and R_9 includ C_{6-12} aromatic hydrocarbons such as phenyl, 1-naphthyl and 2-naphthyl, 5- to 10-membered aromatic heterocyclic groups which contain 1 to 4 hetero atoms of O, S, and N (e.g. furyl, thienyl, thiazolyl, pyridyl and pyranyl), and these aromatic groups as condensed with another aromatic ring such as a benzene ring, such as indolyl, quinolyl and quinoxalyl. These alkyl groups, cycloalkyl groups and aromatic cyclic groups may have 1 to 3 additional substituents. Example substituents for the alkyl group include C_{3-8} cycloalkyls (e.g., cyclopentyl, cyclohexyl), C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy), C_{1-6} alkylthios (e.g., methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, tert-butylthio), hydroxyl, carboxyl, C_{1-6} alkylcarbonyls (e.g., formyl, acetyl), aromatic cyclic groups (e.g., C_{6-12} aromatic hydrocarbon groups which may be substituted by a halogen atom, hydroxy group, C_{1-3} alkoxy group or C_{1-3} alkyl group such as phenyl, fluorophenyl, chlorophenyl, bromophenyl, hydroxyphenyl, methoxyphenyl, methylphenyl, 1-naphthyl and 2-naphthyl, and 5- to 10- membered aromatic heterocyclic groups which contain 1 to 4 hetero atoms of O, S, and N such as furyl, thienyl, thiazolyl, indolyl, pyridyl, pyranyl, imidazolyl, pyrimidyl and quinolyl). Example of the substituents for the cycloalkyl group include C_{1-6} alkyls (e.g., methyl, ethyl, n-propyl, n-butyl), C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy), C_{1-6} alkylthios (e.g., methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, tert-butylthio), hydroxy, carboxyl, C_{1-6} alkylcarbonyls (e.g., formyl, acetyl). Example substituents for the aromatic cyclic group on carbon atoms include C_{1-6} alkyls (e.g., methyl, ethyl, n-propyl, n-butyl), C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, n-butoxy), hydroxyl, carboxyl, C_{1-6} alkyl (e.g., formyl, acetyl). Example substituents for the aromatic cyclic group on nitrogen atoms include C_{1-6} alkyls (e.g., methyl, ethyl, n-propyl, n-butyl). The di-substituted amino groups (R_8R_9N-) also include those wherein R_8 and R_9 bind together to form a ring. Examples of the ring which R_8 and R_9 bind together to form include a 5- to 9- membered nitrogen-containing heterocyclic ring which may have 1 or 2 hetero atoms such as oxygen atom and sulfur atom. Examples of the nitrogen-containing heterocyclic ring include pyrrolidinyl, piperidinyl, hexamethyleneiminyl, heptamethyleneiminyl, oxazolidinyl, morphonyl, thiazolidinyl, thiomorphonyl, imidazolidinyl, piperazinyl, pyrrolyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 2-oxazolidonyl, 2-thiazolidonyl, imidazolyl, 1,4,5,6-tetrahydropyrimidinyl, 2-3-dihydro-1H-indolyl, 1,2,3,4-tetrahydroquinolinyl, 2,3,4,5-tetrahydro-1H-1-benzazepinyl, 2,3-dihydro-1H-isoindolyl, 1,2,3,4-tetrahydroisoquinolyl, 2,3,4,5-tetrahydro-1H-2-benzazepinyl, 2,3,4,5-tetrahydro-1H-3-benzazepinyl, 1,2,3,4,5,6-hexahydro-1-benzazocinyl, 1,2,3,4,5,6-hexahydro-2-benzazocinyl, 1,2,3,4,5,6-hexahydro-3-benzazocinyl, 2,3,4,5,6,7-hexahydro-1H-1-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-2-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-3-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-4-benzazonyl, β-carbolynyl, phenoxadinyl, phenothiadinyl, 3H-3-benzazepinyl, 3,4-dihydroquinolyl, benzimidanyl, 1,4-benzodiazepinyl, 10,11-dihydro-5H-dibenz (b,f) azepine-5-yl. The preferable examples include a hexamethyleneiminyl, 10,11-dihydro-5H-dibenz (b,f) azepine-5-yl, morphonyl, piperidinyl, piperadinyl.

These nitrogen-containing heterocyclic rings may have 1 to 3 substituents.

Examples of the substituents include a C_{1-6} alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl), a phenyl group, a halogen atom (e.g. fluoro, chloro, bromo, iodo), a nitro group, a cyano group, a hydroxy group, a C_{1-4} alkoxy group (e.g. methoxy, ethoxy, n-propoxy, n-butoxy, isopropoxy), a C_{1-4} alkylthio group (e.g. methylthio, ethylthio, propylthio, isopropylthio), an amino group, a mono- or di-C_{1-4} alkylamino group (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino), a C_{1-4} alkylcarbonylamino group (e.g. formylamino, acetylamino, propyonylamino, butylylamino), a C_{1-4} alkylsulfonylamino group (e.g. methylsulfonylamino, ethylsulfonylamino), a C_{1-4} alkoxycarbonyl group (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl), a carboxyl group, a C_{1-6} alkylcarbonyl group (e.g. formyl, methylcarbonyl, ethylcarbonyl, propylcarbonyl), a C_{1-4} alkylcarbonyloxy group (e.g. acetyl, ethylcarbonyloxy), a 5- or 6- membered heterocyclic group having 1 to 4 hetero atoms such as O, S, and N (e.g. pyridinyl, furyl, thiophenyl). More preferable mono-substituted amino groups (R_7NH-) include cyclohexylamino, phenylamino (anilino) and benzylamino. More preferable di-substituted amino groups (R_8R_9N-) include dicylohexylamino, diphenylamino, hexamethyleneimino (homopiperidino), 10,11-dihydro-5H-dibenz(b,f)azepin-5-yl(Dba), morpholino, piperidino, methylpiperazino and 1-(2-pyrimidyl) piperazino.

With respect to formula [I], R_2 and R_5 independently represent a hydrogen atom or a lower alkyl group. The lower alkyl group is a straight or branched alkyl group having 1 to 6 carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl and n-hexyl. For R_2 and R_5, a hydrogen atom or C_{1-3} alkyl group such as a methyl is particularly preferable.

With respect to formula [I], R_3 represents an aliphatic group which may have an oxygen atom or a sulfur atom. The aliphatic groups is an alkyl group, a cycloalkyl group or a cycloalkylalkyl group. The methylene (CH_2) in these aliphatic groups at any position other than the a position may be substituted by an oxygen atom or a sulfur atom. The alkyl group is a straight or branched alkyl group having 1 to 8 carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl, n-hexyl, n-heptyl, n-octyl, methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, methylthiomethyl, ethylthiomethyl, 2-methylthioethyl, 2-ethylthioethyl, 3-methylthiopropyl and 3-ethylthiopropyl, with more preference given to alkyl groups having 1 to 6 carbon atoms (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, iso-

amyl, tert-amyl, neopentyl, n-hexyl). The cycloalkyl group is a cycloalkyl group having 3 to 8 carbon atoms, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydrofuran-2-yl and tetrahydrothiophen-2-yl. The cycloalkylalkyl group is a straight or branched alkyl group having 1 to 8 carbon atoms substituted by a cycloalkyl group having 3 to 8 carbon atoms, including cyclopentylmethyl, cyclohexylmethyl, 2-(cyclopentyl)ethyl, 2-(cyclohexyl)ethyl, cyclopentylthiomethyl and cyclohexylthiomethyl. R_3 is preferably a C_{1-6} alkyl group, with greatest preference given to butyl groups (e.g., n-butyl, isobutyl, sec-butyl, tert-butyl). The carbon atom to which R_3 is bound is an asymmetric carbon; compound [I] of the present invention exhibits marked endothelin receptor-antagonistic action because its R_3 is of the L-configuration.

With respect to formula [I], R4 represents a heterocyclic-substituted lower alkyl group which may be substituted.

The heterocyclic-substituted lower alkyl group is a lower alkyl group substituted by a 5- or 6-membered heterocyclic group having 1 to 4 hetero atoms of O, S, and N (e.g., pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, piperidinyl, pyrazolyl, pyrazolidinyl, pyridyl, pyrimidyl, pyradinyl, piperadinyl, pyridazinyl, triazolyl, tetrazolyl, dihydrotriadinyl, pyridyl, oxazolyl, isoxazolyl, oxadiazolyl, morpholinyl, furyl, thienyl, thiazolyl, isothiazolyl, thiazolinyl, thiadiazolyl, triazolidinyl) and these groups as condensed with other rings such as benzene ring (e.g., indolyl, isoindolyl, indolidinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridadinyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl). These heterocyclic groups may have 1 to 3 substituents. Example substituents for the heterocyclic group on carbon atoms include C_{1-6} alkyls (e.g., methyl, ethyl, n-propyl, n-butyl), halogens (e.g., fluorine, chlorine, bromine, iodine), hydroxyl, carboxyl, C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, n-butoxy), C_{1-6} alkylcarbonyls (e.g., formyl, acetyl). Example substituents on nitrogen atoms include C_{1-6} alkyls (e.g., methyl, ethyl, n-propyl, n-butyl), C_{1-6} alkylcarbonyl (e.g., formyl, acetyl) and hydroxy-C_{1-6} alkyls (e.g., hydroxymethyl, 2-hydroxyethyl). The lower alkyl group is a straight or branched alkyl group having 1 to 6 carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl and n-hexyl. Thus, the heterocyclic-substituted lower alkyl group is a heterocyclic-substituted C_{1-6} alkyl group. Examples of such alkyl groups include 2-pyridyl-C_{1-6} alkyls (e.g., 2-pyridylmethyl, 2-(2-pyridyl)ethyl), 3-pyridyl-C_{1-6} alkyls (e.g., 3-pyridilmethyl, 2-(3-pyridyl)ethyl), 4-pyridyl-C_{1-6} alkyls (e.g., 4-pyridilmethyl, 2-(4-pyridyl)ethyl), imidazol-2-yl-C_{1-6} alkyls (e.g., imidazol-2-ylmethyl, 2-(imidazol-2-yl)ethyl), imidazol-4-yl-C_{1-6} alkyls (e.g., imidazol-4-ylmethyl, 2-(imidazol-4-yl)ethyl), indol-3-yl-C_{1-6} alkyls (e.g., indol-3-ylmethyl, 2-(indol-3-yl)ethyl), N-methylindol-3-yl-C_{1-6} alkyls (e.g., N-methylindol-3-ylmethyl, 2-(N-methylindol-3-yl)ethyl), N-ethylindol-3-yl-C_{1-6} alkyls (e.g., N-ethylindol-3-ylmethyl, 2-(N-ethylindol-3-yl)ethyl), N-hydroxymethylindol-3-yl-C_{1-6} alkyls (e.g., N-hydroxymethylindol-3-ylmethyl, 2-(N-hydroxymethylindol-3-yl)ethyl), N-formylindol-3-yl-C_{1-6} alkyls (e.g., N-formylindol-3-ylmethyl, 2-(N-formylindol-3-yl)ethyl), thiazol-4-yl-C_{1-6} alkyls (e.g., thiazol-4-ylmethyl, 2-(thiazol-4-yl)ethyl), and 5-fluoroindol-3-yl-C_{1-6} alkyls (e.g., 5-fluoroindol-3-ylmethyl, 2-(5-fluoroindol-3-yl)ethyl). R_4 is preferably an indol-3-yl-C_{1-6} alkyl which may be substituted, with greatest preference given to indol-3-ylmethyl, N-methylindol-3-ylmethyl, N-hydroxymethylindol-3-ylmethyl etc.

The carbon atom to which R_4 is bound is an asymmetric carbon; compound [I] of the present invention exhibits marked endothelin receptor-antagonistic action because its R4 is of the D-configuration.

With respect to formula [I], X represents a group having an aromatic ring. Specifically, such groups are groups resulting from elimination of one hydrogen atom from the α-amino group of α-amino acids having at least one aromatic cyclic group, and alkylamino groups substituted by an aromatic cyclic group. In other words, it is preferable that CO and X be bound via an amide bond. The aromatic cyclic group is exemplified by aromatic hydrocarbon groups and aromatic heterocyclic groups which may be substituted. Aromatic hydrocarbon groups which may be substituted are C_{6-15} aromatic hydrocarbon groups such as phenyl and α-naphtyl. These aromatic hydrocarbon groups may be substituted by 1 to 3 substituents selected from the group consisting of halogen atoms (ex. fluorine, chlorine, bromine), hydroxy group, C_{1-6} alkyl group (ex. methyl, ethyl), C_{1-6} alkoxy group (ex. methoxy, ethoxy), carboxyl group, C_{1-6} alkylcarbonyl (ex. formyl, acetyl), C_{1-6} alkoxycarbonyl (ex. methoxy carbonyl) and so on. Examples of aromatic hydrocarbon groups which may be substituted are preferably phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methylphenyl, 1-naphthyl, 2-naphthyl. Preferable aromatic heterocyclic groups which may be substituted include 5- or 6-membered aromatic heterocyclic groups having 1 to 4 hetero atoms of O, S, and N and these groups as condensed with other aromatic rings such as a benzene ring (e.g., 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, thiazol-4-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyranyl, indol-3-yl, N-methylindol-3-yl, 2-quinolyl, quinoxalin-2-yl). These aromatic heterocyclic groups may have 1 to 3 substituents which are same as those of the above mentioned aromatic hydrocarbon groups.

In addition to the above-mentioned groups having a substituent, the α-amino acids of α-amino acids having at least one aromatic cyclic group include those protected by a protecting group, and aromatic rings wherein at least one aromatic cyclic group present in the α-amino acid is contained in the substituent or protecting group. Said α-amino acid may be a naturally-occurring α-amino acid (e.g., Gly, Ala, Val, Leu, Ile, Ser, Thr, Glu, Asn, Phe, Trp, Met, His, Cys, Arg, Asn, Gln, Tyr, (I)Tyr, diiodo-Tyr) or a non-naturally-occurring α-amino acid (e.g., Phg, Cha, Nva, Nle, Pya(2), Pya(3), Thi), whether of the L-, D- or DL-configuration. Examples of substituents or protecting groups for the α-amino acid include those present mainly at the 1-carboxyl group thereof, preferably an ester (e.g., benzyl ester, diphenylmethyl

ester, trityl ester) or an amide (e.g., phenylamide, benzylamid , diphenylamide, dibenzylamide, 2-phenylethylamide, 2,2-diphenylethylamide, 1,2-diphenylethylamide, indol-3-ylmethylamide, 2-(indol-3-yl)ethylamide) at th carboxyl group. Examples of the amide at the 1-carboxyl group also include amides with an additional α-amino acid. When there is another carboxyl group in addition to the 1-carboxyl group, the substituent or protective group may be an ester (e.g., phenyl ester, benzyl ester, diphenylmethyl ester, trityl ester) or amide (e.g., phenylamide, benzylamide, diphenylmethylamide, diphenylamide, dibenzylamide, 2-phenylethylamide, 2,2-diphenylethylamide, 1,2-diphenylethylamide, indol-3-ylmethylamide, 2-(indol-3-yl)ethylamide) at that carboxyl group. The substituent or protecting group may also be a substituent or protecting group on a functional group other than the carboxyl group (e.g., hydroxyl group, thiol group, amino group) or a substituent on a carbon atom.

Examples of "groups resulting from elimination of one hydrogen atom from the α-amino acid group of α-amino acids having at least one aromatic ring" for X include -Phe-OH, - Tyr-OH, -Trp-OH, -Phg-OH, -(m-F)Tyr-OH, -(p-F)Phe-OH, -(p-Cl)Phe-OH, -(p-Me)Phe-OH, -Trp(Me)-OH, -Trp(CHO)-OH, -Phe-Trp-OH, -Trp-Phe-OH, -Tyr-Trp-OH, -Trp-Phe-OH, -(m-F)Tyr-(p-F)Phe-OH, -Glu(OBzl)-OH, -Glu-OBzl, -Asp(OBzl)-OH, -Asp-OBzl, -Asp-Asp(OBzl)-OH, -Glu($NBzl_2$)-OH, -Glu(NHBzl)-OH, - Asp($NBzl_2$)-OH, -Asp(NHBzl)-OH, -Glu-$NBzl_2$, -Glu-NHBzl, - Asp-$NBzl_2$, -Asp-NHBzl, -Glu-$NHCHPhCH_2Ph$, -Asp-$NHCHPhCH_2Ph$, -Glu-$NHCH_2CHPh_2$, -Asp-$NHCH_2CHPh_2$, -Glu($NHCHPhCH_2Ph$)-OH, -Asp($NHCHPhCH_2Ph$)-OH, -Glu($NHCH_2CHPh_2$)-OH, -Asp($NHCH_2CHPh_2$)-OH, -Glu($NHCH_2CH_2$-Ind)-OH, -Asp($NHCH_2CH_2$-Ind)-OH, -Glu-$NHCH_2CH_2$-Ind, -Asp-$NHCH_2CH_2$-Ind, -Trp-NH-Ind(OH) and -Tyr-Iqu(OH), -(I)Tyr-Phe-OH, -Trp-Trp-OH, -Tyr(Bzl)-Phe-OH, - Tyr(Bzl)-Trp-OH, -(I)Tyr-Trp-OH, -(I)Tyr-Tyr-OH, -Trp-His-OH, -His-Trp-OH, -Tyr-His-OH, -His-Tyr-OH, -Phe-His-OH, - His-Phe-OH, -Phe-Trp-OH, -Phe-Trp-OH, -Phe-Tyr-OH, -Phe-Phe-OH. The amino acids constituting these groups may be of the L-, D- or DL configuration.

The alkylamino group for the "alkylamino group substituted for by an aromatic cyclic group" for X is specifically a C_{1-10} alkylamino group or a C_{3-10} cycloalkylamino group. The aromatic cyclic group is present as a substituent on carbon or nitrogen of these alkylamino groups (e.g., methylamino, ethylamino, n-propoxylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, n-pentylamino, n-hexylamino, n-decylamino, cyclopropylamino, cyclopentylamino, cyclohexylamino, cyclohexylmethylamino, 2-cyclohexylethylamino). Examples of the aromatic cyclic group are the same as specified above. Thus, "the alkylamino group substituted for by an aromatic cyclic group" is exemplified by-$NBzl_2$, -NEBzl, -$NHCHPhCH_2Ph$, - $NHCH_2CHPh_2$ and -$NHCH_2CH_2$-Ind.

With respect to formula [I], R_6 represents a hydrogen atom, a lower alkyl group which may be substituted or an aromatic cyclic group which may be substituted. The lower alkyl group is a straight or branched alkyl group having 1 to 6 carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl and n-hexyl. These lower alkyl groups may have 1 to 3 substituents. Examples of the substituents include aromatic cyclic groups (e.g., C_{6-15} aromatic hydrocarbon groups and 5- to 6-membered aromatic heterocyclic group which contain 1 to 4 hetero atoms of O, S, and N and these groups as condensed with another aromatic ring (e.g., benzene ring) such as phenyl, naphthyl, indenyl, furyl, thienyl, pyridyl, quinolyl, pyranyl, imidazolyl, pyrimidyl, purinyl, indolyl), sulfur-containing groups (e.g., thione, mercapto, methylthio, ethylthio, phenylthio), oxygen-containing groups (e.g., ketone, hydroxy, methoxy, ethoxy, phenoxy, benzyloxy) and nitrogen-containing groups (e.g., amino, N-methylamino, N-ethylamino, guanidino). The aromatic cyclic group is an aromatic hydrocarbon group or aromatic heterocyclic group which may be substituted. Such an aromatic hydrocarbon group is one having 6 to 12 carbon atoms (e.g., phenyl, 1-naphthyl, 2-naphthyl). The aromatic heterocyclic group is a 5- or 6-membered cyclic group containing 1 to 4 hetero atoms of O, S, and N and these groups as condensed with rings such as benzene ring (e.g., furyl, thienyl, pyridyl, thiazolyl, imidazolyl, indolyl). Examples of substituents for these aromatic hydrocarbon groups or aromatic heterocyclic groups include C_{1-6} alkyls (e.g., methyl, ethyl, n-propyl, n-butyl), halogens (e.g., fluorine, chlorine, bromine, iodine), C_{1-6} alkoxys (e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy), C_{1-6} alkylthios (e.g., methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, tert-butylthio), C_{1-6} alkylcarbonyls (e.g., formyl, acetyl), C_{1-6} alkoxycarbonyls (e.g., methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl). The number of the substituents is 1 to 3. R6 is (i) a C_1-C_6 alkyl group (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isoamyl, tert-amyl, neopentyl or n-hexyl), (ii) 5- to 6-membered aromatic hetero cyclic groups which contain 1 to 4 hetero atoms of O, S, and N (e.g., furyl, thienyl, pyridyl) or (iii) a lower alkyl group substituted by an aromatic heterocyclic group such as a 5- to 6-membered cyclic group which contain 1 to 4 hetero atoms of O, S, and N and the group as condensed with another ring (e.g., benzene ring) such as 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, indol-3-ylmethyl, N-methylindol-3-yl-methyl, N-formylindol-3-ylmethyl 2-thienyl-methyl, 3-thienyl-methyl, 2-imidazolyl-methyl. The carbon atom to which R6 is bound is an asymmetric carbon, which may be of the L-, D- or DL configuration, with preference given to the D-configuration. With respect to formula [I], n represents an integer of 0 or 1 to 4, ideally 0. Provided that n is 0, the -N(R_5)-CH(R_6)-(CH_2)n-CO- moiety is represented by -N(R_5)-CH(R_6)-CO-; therefore, this moiety is an α-amino acid residue (e.g., Ala, Val, Leu, Ile, Trp, Pya(2), Pya(3)), preferably Ala, Trp, Pya(2) or Pya(3). With respect to formula [I], m represents an integer of 2 to 6. -NH-(CH_2)m-CO- represents βAla for m = 2, GABA for m = 3 and εAhx for m = 5.

Peptide [I] of the present invention is structurally unique at the -NH-(CH_2)m-CO-X moiety. By having at least one

aromatic ring at the X moiety, the peptid exhibits marked endothelin receptor-antagonistic action. This contribution of the aromatic ring to endothelin receptor-antagonistic action is evident from comparativ data (IC_{50}) on peptides having an aromatic ring (compounds of Examples) and those having no aromatic ring (compounds of Reference Examples), as described in Test Example given below. Peptide [I] of the present invention includes salts thereof. Such salts are salts with base when [I] is an acidic compound, and salts with acid when [I] is a basic compound. Example salts of peptide [I] with base include alkali metal salts (e.g., sodium salt, potassium salt), alkaline earth metal salts (e.g., calcium salt, magnesium salt), ammonium salt and organic base salts (e.g., pyridine salt, triethylamine salt). Example salts of peptide [I] with acid include inorganic acid salts (e.g., hydrochloride, sulfate, nitrate) and organic acid salts (e.g., acetate, oxalate, p-toluenesulfonate).

Peptide [I] of the present invention can be produced by a known conventional means of peptide production or a method based thereon, whether it is based on solid-phase synthesis or liquid-phase synthesis, for instance. Accordingly, the desired peptide can be produced by condensing the partial peptide or amino acids capable of constituting the peptide represented by formula [I] and the remaining moiety, and when the product has a protected group, deprotecting the product. Example methods of condensation or deprotection include the following methods ① through ⑤:

① M. Bodanszky and M.A. Ondetti, Peptide Synthesis, Interscience Publishers, New York (1966).
② Schroeder and Luebke, The Peptide, Academic Press, New York (1965).
③ N. Izumiya et al., Peputido Gosei no Kiso to Jikken, Maruzen (1975).
④ H. Yajima and S. Sakakibara, Seikagaku Jikken Koza 1, Tanpakusitsu no Kagaku IV, 205 (1977).
⑤ H. Yajima, Zoku Iyakuhin no Kaihatsu, Vol. 14, Peptide Synthesis, Hirokawa Shoten.

After completion of the reaction, ordinary purifying methods such as solvent extraction, distillation, column chromatography, liquid chromatography and recrystallization can be used in combination to purify and isolate peptide [I].

[Effect of the invention]

Peptide [I] of the present invention (including pharmacologically acceptable salts thereof; the same applies below) exhibits endothelin receptor-antagonistic action. The endothelin may, for example, be endothelin-1, -2 or -3 as described in Pharmacia, Vol. 26, pp. 21-24 (1990); the antagonist of the present invention exhibits marked antagonistic action on endothelin-1 and endothelin-2. Peptide [I] is pharmaceutically useful as a prophylactic and therapeutic agent for hypertension, cardiovascular disease and renal disease. For these purposes, peptide [I] may be orally or non-orally administered in the form of a liquid or solid to mammals (e.g., humans, rabbits, dogs, cats, rats, mice). It is a common practice to non-orally administer it in the form of a liquid (e.g., injection). Although the dose volume varies depending on subject, target disease, symptoms, method of administration and other factors, for non-oral use in treating adult hypertension it is advantageous to administer peptide [I] in the form of an injection at about 0.01 to 50 mg, preferably about 0.05 to 20 mg, most preferably 1 to 20 mg, per kg body weight, 1 to 3 times daily by intravenous injection. For oral administration, peptide [I] is administered at about 5 mg to 1 g, preferably about 10 to 100 mg per kg body weight, 1 to 3 times daily. Injections include subcutaneous, intracutaneous, intramuscular and drip infusion injections, as well as intravenous injections. Such injections are prepared by a known method wherein peptide [I] is dissolved, suspended or emulsified in a sterile aqueous or oily solution. Example aqueous solutions for injection include physiological saline and isotonic solutions containing glucose and other auxiliaries, which may be used in combination with appropriate dissolution aids such as alcohols (e.g., ethanol), polyalcohols (e.g., propylene glycol, polyethylene glycol) and nonionic surfactants (e.g., Polysorbate 80, HCO-50). Examples of oily solutions include sesame oil and soybean oil, which may be used in combination with dissolution aids such as benzyl benzoate and benzyl alcohol. The injection thus prepared is usually packaged in an appropriate ampule.

Examples of pharmacologically acceptable salts of peptide [I] which can be used for the endothelin receptor-antagonist of the present invention include alkali metal salts (e.g., sodium salt, potassium salt), alkaline earth metal salts (e.g., calcium salt, magnesium salt), ammonium salts, organic base salts (e.g., pyridine salt, triethylamine salt), inorganic acid salts (e.g., hydrochloride, sulfate, nitrate) and salts of organic acid (e.g., acetate, oxalate, p-toluenesulfonate).

[Examples]

The present invention is hereinafter described in more detail by means of the following working examples, reference examples and a test example. In the examples given below, amino acids are of the L-configuration unless otherwise stated.

The conditions of thin-layer chromatography and HPLC used in the examples are as follows:

(1) Thin-layer chromatography (TLC)

Merck Kiesel Gel $60F_{254}$	
Rf1 chloroform-methanol	95:5
Rf2 chloroform-methanol-acetic acid	90:10:5
Rf3 chloroform-methanol-H_2O	70:30:5

(2) HPLC

Column :	WAKOSIL 5C18 (4.6 × 100 mm)
Eluents :	Eluted on a linear density gradient from solution A to solution B (50 minutes) Solution A (0.1% aqueous solution of trifluoroacetic acid) Solution B (acetonitrile containing 0.1% trifluoroacetic acid)
Flow rate:	1.0 ml/min

Example 1

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Boc-Tyr-OH (1.41 g) and HONB (1.08 g) were dissolved in acetonitrile (20 ml), and WSCD HCl was added under ice cooling conditions, followed by stirring for about 2 hours. To this solution was added an acetonitrile solution (20 ml) containing H-(D)Phe-OBzl HCl (1.31 g) and triethylamine (0.67 ml), followed by stirring for 4 hours. The solvent was distilled off under reduced pressure, the resulting residue was dissolved in ethyl acetate (80 ml), and N,N-diisopropylethylenediamine (0.2 ml) was added, followed by stirring for 10 minutes. Then the mixture was sequentially washed with a saturated sodium hydrogen carbonate solution, 0.2 N hydrochloric acid and pure water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to yield a crystal of Boc-Tyr-(D)Phe-OBzl (2.28 g).

TLC: 0.52 (Rf1), 0.79 (Rf2)

Boc-Tyr-(D)Phe-OBzl (2.08 g) was dissolved in 4 N hydrochloric acid/ethyl acetate (8 ml). After this solution was kept standing at room temperature for 30 minutes, the solvent was distilled off under reduced pressure. The separating crystal was filtered with diethyl ether and dried, after which it was dissolved in N,N-dimethylformamide (10 ml). To this solution were added an acetonitrile solution (10 ml) of Boc-βAla-ONB which had been synthesized from Boc-βAla-OH (0.84 g), HONB (0.88 g) and WSCD • HCl (0.92 g), and triethylamine (0.60 ml), followed by stirring at room temperature overnight. After the solvent was distilled off under reduced pressure, the residue was dissolved in ethyl acetate (80 ml), and N,N-diisopropylethylenediamine (0.4 ml) was added, followed by stirring for 10 minutes. Then the mixture was sequentially washed with a saturated sodium hydrogen carbonate solution, 0.2 N hydrochloric acid and pure water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to yield a crystal of Boc-βAla-Tyr-(D)Phe-OBzl (1.48 g).

TLC: 0.38 (Rf1), 0.76 (Rf2)

Boc-βAla-Tyr-(D)Phe-OBzl (1.47 g) was dissolved in 4 N hydrochloric acid/ethyl acetate (10 ml). After this solution was kept standing at room temperature for 30 minutes, the solvent was distilled off under reduced pressure. The separating crystal was filtered with diethyl ether and dried, after which it was dissolved in N,N-dimethylformamide (10 ml). To this solution were added an acetonitrile solution (10 ml) of Boc-(D)Ala-ONB which had been synthesized from Boc-(D)Ala-OH (0.52 g), HONB (0.54 g) and WSCD • HCl (0.58 g), and triethylamine (0.37 ml), followed by stirring at room temperature overnight. After the solvent was distilled off under reduced pressure, the residue was dissolved in ethyl acetate (80 ml), and N,N-diisopropylethylenediamine (0.4 ml) was added, followed by stirring for 10 minutes. Then the mixture was sequentially washed with a saturated sodium hydrogen carbonate solution, 0.2 N hydrochloric acid and pure water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to yield a crystal of Boc-(D)Ala-βAla-Tyr-(D)Phe-OBzl (1.50 g).

TLC: 0.36 (Rf1), 0.76 (Rf2)

Boc-(D)Ala-βAla-Tyr-(D)Phe-OBzl (1.32 g) was dissolved in 4 N hydrochloric acid/ethyl acetate (10 ml). After this solution was kept standing at room temperature for 30 minutes, the solvent was distilled off under reduced pressure.

The separating crystal was filtered with diethyl ether and dried, after which it was dissolved in N,N-dimethylformamide (10 ml). To this solution were added an acetonitrile solution (10 ml) of Boc-(D)Trp-ONB which had been synthesized from Boc-(D)Trp-OH (0.67 g), HONB (0.43 g) and WSCD • HCl (0.46 g), and triethylamine (0.30 ml), followed by stirring at room temperature overnight. After the solvent was distilled off under reduced pressure, the residue was dissolved in ethyl acetate (80 ml), and N,N-diisopropylethylenediamine (0.4 ml) was added, followed by stirring for 10 minutes. Then the mixture was sequentially washed with a saturated sodium hydrogen carbonate solution, 0.2 N hydrochloric acid and pure water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to yield a crystal of Boc-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl (1.48 g).

TLC: 0.22 (Rf1), 0.75 (Rf2)

Boc-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl (1.27 g) was dissolved in 4 N hydrochloric acid/ethyl acetate (10 ml). After this solution was kept standing at room temperature for 30 minutes, the solvent was distilled off under reduced pressure. The separating crystal was filtered with diethyl ether and dried, after which it was dissolved in N,N-dimethylformamide (10 ml). To this solution were added an acetonitrile solution (10 ml) of Boc-Leu-ONB which had been synthesized from Boc-Leu-OH • H_2O (0.41 g), HONB (0.33 g) and WSCD • HCl (0.35 g), and triethylamine (0.22 ml), followed by stirring at room temperature overnight. After the solvent was distilled off under reduced pressure, the residue was dissolved in ethyl acetate (80 ml), and N,N-diisopropylethylenediamine (0.4 ml) was added, followed by stirring for 10 minutes. Then the mixture was sequentially washed with a saturated sodium hydrogen carbonate solution, 0.2 N hydrochloric acid and pure water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to yield a crystal of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl (1.30 g).

TLC: 0.23 (Rf1), 0.76 (Rf2)

Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl (0.2 g) was dissolved in methanol (50 ml) and then catalytically reduced in a hydrogen stream in the presence of palladium black catalyst. After the catalyst was filtered out and the solvent was distilled off, the residue was dissolved in a 50% aqueous solution of acetic acid (3 ml) and applied to a column (2 × 95 cm) of Sephadex G-25, packed with 50% aqueous acetic acid, and developed with the same solvent. The major fractions were collected and lyophilized to yield a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH (170 mg).

TLC	(Rf2) 0.19, HPLC eluting time 24.6 minutes
Mass analysis:	$(M+H)^+$ = 870

Example 2

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH

Using H-Phe-OBzl • HCl in place of H-(D)Phe-OBzl • HCl in the production in Example 1, the same procedure as in Example 1 was followed to yield 160 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH.

TLC	(Rf2) 0.19, HPLC eluting time 24.6 minutes
Mass analysis:	$(M+H)^+$ = 870

Example 3

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH

Using Boc-(D)Tyr-OH in place of Boc-Tyr-OH in the production in Example 1, the same procedure as in Example 1 was followed to yield 90 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH.

TLC	(Rf2) 0.19, HPLC eluting time 24.4 minutes
Mass analysis:	$(M+H)^+$ = 870

Example 4

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Using Boc-(D)Tyr-OH in place of Boc-Tyr-OH in the production in Example 2, the same procedure as in Example 1 was followed to yield 87 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe.

TLC (Rf2) 0.19, HPLC eluting time 24.6 minutes
Mass analysis: $(M+H)^+ = 870$

Example 5

Production of Boc-Leu-(D)Trp-(D)Ala-εAhx-Tyr-Phe-OH

Using Boc-εAhx-OH in place of Boc-βAla-OH in the production in Example 2, the same procedure as in Example 1 was followed to yield 116 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-εAhx-Tyr-Phe-OH.

TLC (Rf2) 0.20, HPLC eluting time 24.9 minutes
Mass analysis: $(M+H)^+ = 912.1$

Example 6

Production of Boc-Leu-(D)Trp-(D)Trp-βAla-Tyr-Phe-OH

Using Boc-(D)Trp-OH in place of Boc-(D)Ala-OH in the production in Example 2, the same procedure as in Example 1 was followed to yield 106 mg of a white powder of Boc-Leu-(D)Trp-(D)Trp-βAla-Tyr-Phe-OH.

TLC (Rf2) 0.26, HPLC eluting time 26.8 minutes
Mass analysis: $(M+H)^+ = 986.1$

Example 7

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-OH

Using Boc-(D)Tyr-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 126 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-OH.

TLC (Rf2) 0.23, HPLC eluting time 22.2 minutes
Mass analysis: $(M+H)^+ = 723.8$

Example 8

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-OH

Using Boc-Tyr-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 60 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-OH.

TLC (Rf2) 0.23, HPLC eluting time 22.4 minutes
Mass analysis: $(M+H)^+ = 723.7$

Example 9

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Phe-OH

Using Boc-(D)Phe-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 96 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Phe-OH.

TLC (Rf2) 0.24, HPLC eluting time 24.5 minutes

Mass analysis: $(M+H)^+ = 707.8$

Example 10

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Phe-OH

Using Boc-Phe-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 113 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Phe.

TLC (Rf2) 0.24, HPLC eluting time 24.5 minutes
Mass analysis: $(M+H)^+ = 707.8$

Example 11

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)(m-F)Tyr-OH

Using Boc-(D)(m-F)Tyr-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 97 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)(m-F)Tyr-OH.

TLC (Rf2) 0.26, HPLC eluting time 22.5 minutes
Mass analysis: $(M+H)^+ = 741.3$

Example 12

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(m-F)Tyr-OH

Using Boc-(m-F)Tyr-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 108 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(m-F)Tyr-OH.

TLC (Rf2) 0.26, HPLC eluting time 22.5 minutes
Mass analysis: $(M+H)^+ = 741.3$

Example 13

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)(p-F)Phe-OH

Using Boc-(D)(p-F)Phe-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 145 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)(p-F)Phe-OH.

TLC (Rf2) 0.41, HPLC eluting time 24.9 minutes
Mass analysis: $(M+H)^+ = 725.8$

Example 14

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(p-F)Phe-OH

Using Boc-(p-F)Phe-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 89 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(p-F)Phe-OH.

TLC (Rf2) 0.41, HPLC eluting time 24.9 minutes
Mass analysis: $(M+H)^+ = 725.8$

Example 15

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Phg-OH

Using Boc-(D)Phg-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 49 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Phg-OH.

TLC (Rf2) 0.24, HPLC eluting time 24.1 minutes
Mass analysis: $(M+H)^+ = 693.3$

Example 16

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-OH

Using Boc-Trp-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 198 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-OH.

TLC (Rf2) 0.27, HPLC eluting time 24.3 minutes
Mass analysis: $(M+H)^+ = 746.3$

Example 17

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Trp-OH

Using H-(D)Trp-OBzl • HCl in place of H-(D)Phe-OBzl • HCl in the production in Example 1, the same procedure as in Example 1 was followed to yield 160 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Trp-OH.

TLC (Rf2) 0.19, HPLC eluting time 27.0 minutes
Mass analysis: $(M+H)^+ = 909.5$

Example 18

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-(D)Phe-OH

Using Boc-Trp-OH in place of Boc-Tyr-OH in the production in Example 1, the same procedure as in Example 1 was followed to yield 203 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-(D)Phe-OH.

TLC (Rf2) 0.26, HPLC eluting time 26.4 minutes
Mass analysis: $(M+H)^+ = 893.5$

Example 19

Production of Adamantan-1-ylcarbonyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl (0.1 g) was dissolved in 4 N hydrochloric acid/ethyl acetate (1 ml). After this solution was kept standing at room temperature for 30 minutes, the solvent was distilled off under reduced pressure. The residue was filtered with diethyl ether and dried, after which it was dissolved in N,N-dimethylformamide (1 ml). After neutralization of this solution by the addition of triethylamine (15 μ), adamantan-1-ylcarbonyl chloride (25 mg) was added, followed by stirring for 3 hours. After the solvent was distilled off under reduced pressure, the residue was dissolved in ethyl acetate (20 ml) and sequentially washed with a saturated sodium hydrogen carbonate solution, 0.2 N hydrochloric acid and pure water, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to yield a powder of adamantan-1-ylcarbonyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl (0.1 g). This powder was dissolved in methanol (50 ml) and then catalytically reduced in a hydrogen stream in the presence of palladium black catalyst. After the catalyst was filtered out and the solvent was distilled off, the residue was dissolved in a 50% aqueous solution of acetic acid (3 ml) and applied to a column (2 × 95 cm) of 50% Sephadex G-25, packed with 50% aqueous acetic acid, and developed with the same solvent. The major fractions were collected and lyophilized to yield a white powder of adamantan-1-ylcarbonyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH (70 mg).

TLC (Rf2) 0.22, HPLC eluting time 26.7 minutes
Mass analysis: $(M+H)^+ = 932.5$

Example 20

Production of Adamantan-1-ylcarbonyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH

Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OBzl was reacted in the same manner as in Example 19 to yield 50 mg of a white powder of adamantan-1-ylcarbonyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe.

TLC	(Rf2) 0.22, HPLC eluting time 26.7 minutes
Mass analysis:	$(M+H)^+$ = 932.4

Example 21

Production of (1S)-(-)-Camphanyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl was reacted with (1S)-(-)-Camphanyl chloride in the same manner as in Example 19 to yield 50 mg of a white powder of (1S)-(-)-Camphanyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC	(Rf2) 0.23, HPLC eluting time 26.5 minutes
Mass analysis:	$(M+H)^+$ = 951.1

Example 22

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu(OBzl)-OH

Using Boc-Glu(OBzl)-OPac in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield Boc-Leu-(D)Trp-(D)Ala-βAla-Glu(OBzl)-OPac, which was dissolved in 90% acetic acid and treated with zinc powder at room temperature for 1 hour, after which it was applied to a column (2 × 95 cm) of Sephadex G-25, packed with 50% aqueous acetic acid, and developed with the same solvent. The major fractions were collected and lyophilized to yield a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu(OBzl)-OH (30 mg).

TLC	(Rf2) 0.20, HPLC eluting time 25.3 minutes
Mass analysis:	$(M+H)^+$ = 779.2

Example 23

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-OBzl

Using Boc-Glu(OPac)-OBzl in place of Boc-Glu(OBzl)-OPac in the production in Example 22, the same procedure as in Example 22 was followed to yield 53 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-OBzl.

TLC	(Rf2) 0.19, HPLC eluting time 25.1 minutes
Mass analysis:	$(M+H)^+$ = 779.2

Example 24

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Asp(OBzl)-OH

Using Boc-(D)Asp(OBzl)-OPac in place of Boc-Glu(OBzl)-OPac in the production in Example 22, the same procedure as in Example 22 was followed to yield 59 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Asp(OBzl)-OH.

TLC	(Rf2) 0.19, HPLC eluting time 25.7 minutes
Mass analysis:	$(M+H)^+$ = 765.1

Example 25

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Asp-OBzl

Using Boc-(D)Asp(OPac)-OBzl in place of Boc-Glu(OBzl)-OPac in the production in Example 22, the same proce-

dure as in Example 22 was followed to yield 65 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Asp-OBzl.

TLC	(Rf2) 0.19, HPLC eluting time 25.7 minutes
Mass analysis:	$(M+H)^+$ = 765.1

Example 26

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-NHCHPhCH$_2$Ph

Using Boc-Glu(OBzl)-NHCHPhCH$_2$Ph which had been synthesized from Boc-Glu(OBzl)-OH and 1,2-diphenylethylamine in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 45 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-NHCHPhCH$_2$Ph.

TLC	(Rf2) 0.25, HPLC eluting time 26.9 minutes
Mass analysis:	$(M+H)^+$ = 868.6

Example 27

Production of Boc-Leu-(D)Trp-(D)Ala-εAhx-Glu-NHCH$_2$CHPh$_2$

Using Boc-Glu(OBzl)-NHCH$_2$CHPh$_2$ which had been synthesized from Boc-Glu(OBzl)-OH and 2,2-diphenylethylamine in place of Boc-Tyr-Phe-OBzl in the production in Example 5, the same procedure as in Example 1 was followed to yield 64 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-εAhx-Glu-NHCH$_2$CHPh$_2$.

TLC	(Rf2) 0.27, HPLC eluting time 26.9 minutes
Mass analysis:	$(M+H)^+$ = 910.6

Example 28

Production of Boc-Leu-(D)Trp-(D)Ala-εAhx-Asp-NHCHPhCH$_2$Ph

Using Boc-Asp(OBzl)-NHCHPhCH$_2$Ph which had been synthesized from Boc-Asp(OBzl)-OH and 1,2-diphenylethylamine in place of Boc-Glu(OBzl)-NHCH$_2$CHPh$_2$ in the production in Example 27, the same procedure as in Example 1 was followed to yield 66 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-εAhx-Asp-NHCHPhCH$_2$Ph.

TLC	(Rf2) 0.27, HPLC eluting time 26.7 minutes
Mass analysis:	$(M+H)^+$ = 896.9

Example 29

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp-NHCH$_2$CHPh$_2$

Using Boc-Asp(OBzl)-NHCH$_2$CHPh$_2$ which had been synthesized from Boc-Asp(OBzl)-OH and 2,2-diphenylethylamine in place of Boc-Glu(OBzl)-NHCHPhCH$_2$Ph in the production in Example 26, the same procedure as in Example 1 was followed to yield 78 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp-NHCH$_2$CHPh$_2$.

TLC	(Rf2) 0.28, HPLC eluting time 26.6 minutes
Mass analysis:	$(M+H)^+$ = 854.9

Example 30

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp-NHCH$_2$CH$_2$-Ind

Using Boc-Asp(OBzl)-NHCH$_2$CH$_2$-Ind which had been synthesized from Boc-Asp(OBzl)-OH and 2-(indol-3-yl)ethylamine in place of Boc-glu(OBzl)-NHCHPhCH$_2$Ph in the production in Example 26, the same procedure as in Example 1 was followed to yield 115 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp-NHCH$_2$CH$_2$-Ind.

TLC	(Rf2) 0.17, HPLC eluting time 24.5 minutes

Mass analysis: $(M+H)^+$ = 817.9

Example 31

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp($NHCH_2CH_2$-Ind)

Using Boc-Asp($NHCH_2CH_2$-Ind)-OBzl in place of Boc-Asp(OBzl)-$NHCH_2CH_2$-Ind in the production in Example 30, the same procedure as in Example 1 was followed to yield 86 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp($NHCH_2CH_2$-Ind).

TLC (Rf2) 0.18, HPLC eluting time 24.5 minutes
Mass analysis: $(M+H)^+$ = 817.8

Example 32

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-Asp($NBzl_2$)-$NHCH_2CH_2$-Ind

Using Boc-Glu(OBzl)-Asp($NBzl_2$)-$NHCH_2CH_2$-Ind in place of Boc-Asp(OBzl)-$NHCH_2CH_2$-Ind in the production in Example 30, the same procedure as in Example 1 was followed to yield 100 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-Asp($NBzl_2$)-$NHCH_2CH_2$-Ind.

TLC (Rf2) 0.25, HPLC eluting time 28.8 minutes
Mass analysis: $(M+H)^+$ = 1125.9

Example 33

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-Asp($NHCH_2CH_2$-Ind)-$NBzl_2$

Using Boc-Glu(OBzl)-Asp($NHCH_2CH_2$-Ind)-$NBzl_2$ in place of Boc-Asp($NHCH_2CH_2$-Ind)-OBzl in the production in Example 31, the same procedure as in Example 1 was followed to yield 92 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-Asp($NHCH_2CH_2$-Ind)-$NBzl_2$.

TLC (Rf2) 0.26, HPLC eluting time 28.8 minutes
Mass analysis: $(M+H)^+$ = 1126.0

Example 34

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp-$NBzl_2$

Using Boc-Asp(OBzl)-$NBzl_2$ in place of Boc-Asp(OBzl)-$NHCH_2CH_2$-Ind in the production in Example 30, the same procedure as in Example 1 was followed to yield 68 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Asp-$NBzl_2$.

TLC (Rf2) 0.21, HPLC eluting time 26.9 minutes
Mass analysis: $(M+H)^+$ = 854.4

Example 35

Production of Boc-Leu-(D)Trp-(D)Ala-GABA-Tyr-Phe-OH

Using Boc-GABA-OH in place of Boc-βAla-OH in the production in Example 2, the same procedure as in Example 1 was followed to yield 160 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-GABA-Tyr-Phe-OH.

TLC (Rf2) 0.20, HPLC eluting time 24.8 minutes
Mass analysis: $(M+H)^+$ = 884.9

Example 36

Production of Boc-Leu-(D)Trp-(D)Ala-εAhx-$NHCHPhCH_2Ph$

Using 1,2-diphenylethylamine in place of H-Tyr-Phe-OBzl in the production in Example 5, the same procedure as in Example 1 was followed to yield 89 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-εAhx-$NHCHPhCH_2Ph$ without catalytic reduction.

TLC	(Rf2) 0.32, HPLC eluting time 28.5 minutes
Mass analysis:	$(M+H)^+ = 781.4$

Example 37

Production of Boc-Leu-(D)Trp-(D)Ala-εAhx-$NHCH_2CHPh_2$

Using 2,2-diphenylethylamine in place of 1,2-diphenylethylamine in the production in Example 36, the same procedure as in Example 36 was followed to yield 91 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-εAhx-$NHCH_2CHPh_2$.

TLC	(Rf2) 0.32, HPLC eluting time 28.4 minutes
Mass analysis:	$(M+H)^+ = 781.4$

Example 38

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(m-F)Tyr-(p-F)Phe-OH

Using Boc-(m-F)Tyr-OH and H-(p-F)Phe-OBzl • HCl in place of Boc-Tyr-OH and H-(D)Phe-OBzl • HCl, respectively, in the production in Example 1, the same procedure as in Example 1 was followed to yield 106 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(m-F)Tyr-(p-F)Phe-OH.

TLC	(Rf2) 0.22, HPLC eluting time 25.1 minutes
Mass analysis:	$(M+H)^+ = 906.5$

Example 39. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using hexamethyleneimino-CO-Leu-OH produced from hexamethyleneimino-CO-Leu-OBzl, which can be produced from hexamethyleneimine and N-carbonyl-Leu-OBzl or from hexamethyleneimine, Leu-OBzl and carbonyldiimidazole, in place of Boc-Leu-OH • H_2O in the production in Example 1, the corresponding amine component (H-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl) of Example 1 and triethylamine were dissolved in N,N-dimethylformamide, and this solution was condensed with HONB and WSCD • HCl to yield hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl, which was treated in the same manner as with Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl in Example 1 to yield 62 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.18 (Rf2), 0.44 (Rf3)
HPLC eluting time:	24.2 minutes
Mass analysis:	$(M+H)^+ = 895.4$

Example 40. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-ONa

Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl as described in Example 39 was dissolved in methanol (1 mmole/45 ml), and the ester was hydrolyzed with a 5-fold amount of 1 N-NaOH. After neutralizing the excess alkali with a 4-fold amount of 1 N-HCl, the solvent was distilled off under reduced pressure. The residue was diluted to about 10^{-2} M with distilled water and then applied to a column of Diaion HP-20. After the column was thoroughly washed with distilled water, elution was conducted with 80% aqueous methanol. The desired fraction was collected and concentrated and then subjected to column chromatography using a column of Sephadex LH-20, packed using 50% methanol; the major fraction was collected and lyophilized to yield 50 mg of a white powder. Na content determined by atomic absorption spectrometry: 2.5%

Example 41. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH

Using H-(D)Trp-(D)Ala-βlAla-Tyr-Phe-OBzl, the intermediate used in the production in Example 2, in place of the amine component H-(D)Trp-(D)Ala-βlAla-Tyr-(D)Phe-OBzl in the production in Example 39, the same procedure as in Example 39 was followed to yield 120 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH.

TLC:	0.24 (Rf2), 0.44 (Rf3)
HPLC eluting time:	24.2 minutes
Mass analysis:	$(M+H)^+$ = 895.4

Example 42. Production of Hexamethyleneimino-CO-Leu-(D)Trp-Ala-βAla-Tyr-(D)Phe-OH

Using H-(D)Trp-Ala-βlAla-Tyr-(D)Phe-OBzl, the intermediate prepared using Boc-Ala-OH in place of Boc-(D)Ala-OH in the production in Example 1, in place of the amine component H-(D)Trp-(D)Ala-βlAla-Tyr-(D)Phe-OBzl in the production in Example 39, the same procedure as in Example 39 was followed to yield 35 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.22 (Rf2), 0.45 (Rf3)
HPLC eluting time:	24.3 minutes
Mass analysis:	$(M+H)^+$ = 895.4

Example 43. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr(I)-(D)Phe-OH

Using H-(D)Trp-(D)Ala-βAla-Tyr(I)-(D)Phe-OBzl, the intermediate prepared using Boc-Tyr(I)-OH in place of Boc-Tyr-OH in the production in Example 1, in place of the amine component H-(D)Trp-(D)Ala-βlAla-Tyr-(D)Phe-OBzl in the production in Example 39, the same procedure as in Example 39 was followed to yield hexamethyleneimino-CO-Leu-(D)Trp-Ala-βAla-Tyr-(D)Phe-OBzl, which was dissolved in methanol, and the ester was hydrolyzed with a 5-fold amount of 1 N-NaOH. After neutralization with a 5-fold amount of 1 N-HCl, the solvent was distilled off under reduced pressure. The residue was applied to a column (2 × 95 cm) of Sephadex G-25, packed using 50% aqueous acetic acid, and developed with the same solvent. The major fraction was collected and lyophilised to yield 72 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr(I)-(D)Phe-OH.

TLC:	0.21 (Rf2)
HPLC eluting time:	25.7 minutes
Mass analysis:	$(M+H)^+$ = 1021.4

Example 44. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Thg(2)-βAla-Tyr-(D)Phe-OH

Using H-(D)Trp-(D)Thg(2)-βAla-Tyr-(D)Phe-OBzl, the intermediate prepared using Boc-(D)Thg(2)-OH in place of Boc-(D)Ala-OH in the production in Example 1, in place of the amine component H-(D)Trp-(D)Ala-βlAla-Tyr-(D)Phe-OBzl in the production in Example 39, the same procedure as in Example 39 was followed to yield hexamethyleneimino-CO-Leu-(D)Trp-(D)Thg(2)-βAla-Tyr-(D)Phe-OBzl, which was subjected to the same ester hydrolysis and purification procedures as in Example 43 to yield 80 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Thg(2)-βAla-Tyr-(D)Phe-OH.

TLC:	0.20 (Rf2)
HPLC eluting time:	25.5 minutes
Mass analysis:	$(M+H)^+$ = 963.5

Example 45. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Thg(3)-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Thg(3)-OH in place of Boc-(D)Thg(2)-OH in the production in Example 44, the same procedure as in Example 44 was followed to yield 45 mg of a white powder in hexamethyleneimino-CO-Leu-(D)Trp-(D)Thg(3)-βAla-Tyr-(D)Phe-OH.

TLC:	0.20 (Rf2)
HPLC eluting time:	25.6 minutes

Mass analysis: $(M+H)^+$ = 963.5

Example 46. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Thi-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Thi-OH in place of Boc-(D)Thg(2)-OH in the production in Example 44, the same procedure as in Example 44 was followed to yield 45 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Thi-βAla-Tyr-(D)Phe-OH.

TLC:	0.23 (Rf2), 0.52 (Rf3)
HPLC eluting time:	26.1 minutes
Mass analysis:	$(M+H)^+$ = 977.4

Example 47. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-εAhx-OH

Using the amine component obtained using H-(D)Phe-εAhx-OBzl • HCl produced from Boc-(D)Phe-OH and H-εAhx-OBzl • HCl in place of H-(D)Phe-OBzl • HCl in the production in Example 1, the same procedure as in Example 39 was followed to yield 72 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-εAhx-OH.

TLC:	0.33 (Rf2)
HPLC eluting time:	24.1 minutes
Mass analysis:	$(M+H)^+$ = 1008.4

Example 48. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-βAla-OH

Using the amine component obtained using H-(D)Phe-βAla-OBzl • HCl produced from Boc-(D)Phe-OH and H-βAla-OBzl • HCl in place of H-(D)Phe-OBzl • HCl in the production in Example 1, the same procedure as in Example 39 was followed to yield 68 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-βAla-OH.

TLC:	0.22 (Rf2)
HPLC eluting time:	23.4 minutes
Mass analysis:	$(M+H)^+$ = 966.5

Example 49. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OH

Using H-(D)Trp-(D)Ala-βlAla-Trp-NH-Ind-OCH_3, the intermediate prepared using Boc-Trp-OH and NH_2-Ind-OCH_3 in place of Boc-Tyr-OH and H-(D)Phe-OBzl • HCl, respectively, in the production in Example 1, in place of the amine component H-(D)Trp-(D)Ala-βlAla-Tyr-(D)Phe-OBzl in the production in Example 39, the same procedure as in Example 39 was followed to yield hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OCH_3, which was subjected to the same ester hydrolysis and purification procedures as in Example 43 to yield 30 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OH.

TLC:	0.30 (Rf2)
HPLC eluting time:	26.2 minutes
Mass analysis:	$(M+H)^+$ = 930.4

Example 50. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Iqu-(D)Trp-OH

Using H-(D)Trp-(D)Ala-βlAla-Iqu-(D)Trp-OCH_3, the intermediate prepared using Boc-Iqu-OH and H-(D)Trp-OCH_3 • HCl in place of Boc-Tyr-OH and H-(D)Phe-OBzl • HCl, respectively, in the production in Example 1, in place of the amine component H-(D)Trp-(D)Ala-βlAla-Tyr-(D)Phe-OBzl in the production in Example 39, the same procedure as in Example 39 was followed to yield hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Iqu-(D)Trp-OCH_3, which was subjected to the same ester hydrolysis and purification procedures as in Example 43 to yield 43 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Iqu-(D)Trp-OH.

TLC:	0.25 (Rf2), 0.55 (Rf3)
HPLC eluting time:	26.3 minutes
Mass analysis:	$(M+H)^+$ = 930.4

Example 51. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)His-βAla-Tyr-(D)Phe-OH

Using H-(D)Trp-(D)His-βlAla-Tyr-(D)Phe-OBzl, the intermediate prepared using Boc-(D)His(Boc)-OH in plac of Boc-(D)Ala-OH in the production in Example 1, in place of the amine component H-(D)Trp-(D)Ala-βlAla-Tyr-(D)Phe-OBzl in the production in Example 39, the same procedure as in Example 39 was followed to yield 30 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)His-βAla-Tyr-(D)Phe-OH.

TLC:	0.49 (Rf3)
HPLC eluting time:	22.8 minutes
Mass analysis:	$(M+H)^+ = 961.6$

Example 52. Production of Cyclohexyl-NH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using cyclohexyl isocyanate in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 54 mg of a white powder of cyclohexyl-NH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.17 (Rf2)
HPLC eluting time:	24.3 minutes
Mass analysis:	$(M+H)^+ = 895.4$

Example 53. Production of Dicyclohexyl-NH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using dicyclohexylamine in place of hexamethyleneimine in the production in Example 39, the same procedure as in Example 39 was followed to yield 73 mg of a white powder of dicyclohexyl-NH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.20 (Rf2)
HPLC eluting time:	24.8 minutes
Mass analysis:	$(M+H)^+ = 977.6$

Example 54. Production of Me-Pip-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using 1-methylpiperazine in place of hexamethyleneimine in the production in Example 39, the same procedure as in Example 39 was followed to yield 84 mg of a white powder of Me-Pip-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.28 (Rf3)
HPLC eluting time:	20.8 minutes
Mass analysis:	$(M+H)^+ = 896.2$

Example 55. Production of Pym-Pip-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using 1-(2-pyrimidyl)piperazine in place of hexamethyleneimine in the production in Example 39, the same procedure as in Example 39 was followed to yield 55 mg of a white powder of Pym-Pip-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.14 (Rf2), 0.49 (Rf3)
HPLC eluting time:	22.0 minutes
Mass analysis:	$(M+H)^+ = 960.5$

Example 56. Production of $PhCH_2NH$-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using benzylamine in place of hexamethyleneimine in the production in Example 39, the same procedure as in Example 39 was followed to yield 91 mg of a white powder of $PhCH_2NH$-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

Mass analysis: $(M+H)^+ = 903.5$

Example 57. Production of 2-Furyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using 2-furoyl chloride in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 70 mg of a white powder of 2-furyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.09 (Rf2)
HPLC eluting time:	22.8 minutes
Mass analysis:	$(M+H)^+ = 864.4$

Example 58. Production of 2-Thienyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using 2-thiophenecarbonyl chloride in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 87 mg of a white powder of 2-thienyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.10 (Rf2)
HPLC eluting time:	23.4 minutes
Mass analysis:	$(M+H)^+ = 880.3$

Example 59. Production of Quinoxalin-2-yl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using 2-quinoxaloyl chloride in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 59 mg of a white powder of quinoxalin-2-yl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

Mass analysis: $(M+H)^+ = 927.4$

Example 60. Production of Benzoyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using benzoyl chloride in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 124 mg of a white powder of benzoyl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

Mass analysis: $(M+H)^+ = 874.4$

Example 61. Production of Ph_2N-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using diphenylcarbamoyl chloride in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 34 mg of a white powder of Ph_2N-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.14 (Rf2)
HPLC eluting time:	26.6 minutes
Mass analysis:	$(M+H)^+ = 965.5$

Example 62. Production of PhNH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using phenyl isocyanate in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 39 mg of a white powder of PhNH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

Mass analysis: $(M+H)^+ = 889.5$

Example 63. Production of Tetrahydronaphthalene-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OBzl (0.1 g) was dissolved in 4 N hydrochloric acid/ethyl acetate (1 ml), and the resulting solution was kept standing at room temperature for 30 minutes. After the solvent was distilled off under

reduced pressure, the residue was filtered with diethyl ether and dried, after which it was dissolved in N,N-dimethylformamide (1 ml). After this solution was neutralized with triethylamin (15 μl), 1,2,3,4-tetrahydro-2-naphthoic acid (17 mg), HOBt (15 mg) and WSCD • HCl (22 mg) were added, followed by stirring at room temperature overnight. The mixture was treated in the sam manner as in Example 19 to yield 37 mg of a white powder of tetrahydronaphthalene-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.15 (Rf2)
HPLC eluting time:	25.5 minutes
Mass analysis:	$(M+H)^+ = 928.5$

Example 64. Production of 2, 2-Dimethylbutyryl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using 2,2-dimethylbutyric acid in place of 1,2,3,4-tetrahydro-2-naphthoic acid in the production in Example 63, the same procedure as in Example 63 was followed to yield 33 mg of a white powder of 2,2-dimethylbutyryl-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.19 (Rf2)
HPLC eluting time:	24.6 minutes
Mass analysis:	$(M+H)^+ = 868$

Example 65. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Pya(2)-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Pya(2)-OH in place of Boc-(D)Ala-OH in the production in Example 39, the same procedure as in Example 39 was followed to yield 21 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Pya(2)-βAla-Tyr-(D)Phe-OH.

TLC:	0.07 (Rf2)
HPLC eluting time:	23.1 minutes
Mass analysis:	$(M+H)^+ = 972.4$

Example 66. Production of Hexamethyleneimino-CO-Leu-(D)Trp-(D)Pya(3)-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Pya(3)-OH in place of Boc-(D)Ala-OH in the production in Example 39, the same procedure as in Example 39 was followed to yield 27 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp-(D)Pya(3)-βAla-Tyr-(D)Phe-OH.

TLC:	0.07 (Rf2)
HPLC eluting time:	23.1 minutes
Mass analysis:	$(M+H)^+ = 927.4$

Example 67. Production of Hexamethyleneimino-CO-Leu-(D)Trp(Me)-(D)Ala-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Trp(Me)-OH in place of Boc-(D)Trp-OH in the production in Example 39, the same procedure as in Example 39 was followed to yield 58 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp(Me)-(D)Ala-βAla-Tyr-(D)Phe- OH.

TLC:	0.22 (Rf2)
HPLC eluting time:	24.7 minutes
Mass analysis:	$(M+H)^+ = 909.4$

Example 68. Production of Hexamethyleneimino-CO-Leu-(D)Trp(Me)-(D)Pya(2)-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Trp(Me)-OH and Boc-(D)Pya(2)-OH in place of Boc-(D)Trp-OH and Boc-(D)Ala-OH, respectively, in the production in Example 39, the same procedure as in Example 39 was followed to yield 28 mg of a white powder of hexamethyleneimino-CO-Leu-(D)Trp(Me)-(D)Pya(2)-βAla-Tyr-(D)Phe-OH.

TLC:	0.18 (Rf2)
HPLC eluting time:	24.5 minutes

Mass analysis: $(M+H)^+$ = 986.4

Example 69. Production of Boc-Leu-(D)Trp(Me)-(D)Ala-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Trp(Me)-OH in place of Boc-(D)Trp-OH in the production in Example 1, the same procedure as in Example 1 was followed to yield 39 mg of a white powder of Boc-Leu-(D)Trp(Me)-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC: 0.27 (Rf2)
HPLC eluting time: 25.8 minutes
Mass analysis: $(M+H)^+$ = 884

Example 70. Production of Boc-Leu-(D)Trp-(D)Pya(2)-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Pya(2)-OH in place of Boc-(D)Ala-OH in the production in Example 1, the same procedure as in Example 1 was followed to yield 59 mg of a white powder of Boc-Leu-(D)Trp-(D)Pya(2)-βAla-Tyr-(D)Phe-OH.

TLC: 0.07 (Rf2)
HPLC eluting time: 23.4 minutes
Mass analysis: $(M+H)^+$ = 947.4

Example 71. Production of Boc-Leu-(D)Trp-(D)Pya(3)-βAla-Tyr-(D)Phe-OH

Using Boc-(D)Pya(3)-OH in place of Boc-(D)Ala-OH in the production in Example 1, the same procedure as in Example 1 was followed to yield 43 mg of a white powder of Boc-Leu-(D)Trp-(D)Pya(3)-βAla-Tyr-(D)Phe-OH.

TLC: 0.07 (Rf2)
HPLC eluting time: 23.4 minutes
Mass analysis: $(M+H)^+$ = 947.4

Example 72. Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OH

Using Boc-Trp-OH and H-NH-Ind-OCH_3 • HCl in place of Boc-Tyr-OH and H-(D)Phe-OBzl • HCl, respectively, in the production in Example 1, the same procedure as in Example 1 was followed to yield Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OCH_3, which was subjected to the same ester hydrolysis and purification procedures as in Example 64 to yield 75 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OH.

TLC: 0.26 (Rf2), 0.67 (Rf3)
HPLC eluting time: 26.2 minutes
Mass analysis: $(M+H)^+$ = 905.4

Example 73. Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-(D)Trp-OH

Using H-(D)Trp-OCH_3 • HCl in place of H-(D)Phe-OBzl • HCl in the production in Example 1, the same procedure as in Example 1 was followed to yield Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-(D)Trp-OCH_3, which was subjected to the same ester hydrolysis and purification procedures as in Example 43 to yield 75 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Trp-(D)Trp-OH.

TLC: 0.14 (Rf2)
HPLC eluting time: 26.0 minutes
Mass analysis: $(M+H)^+$ = 932

Example 74. Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr(Bzl)-(D)Trp-OH

Using Boc-Trp-OH in place of Boc-Tyr-OH in the production in Example 73, the same procedure as in Example 43 was followed to yield 75 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr(Bzl)-(D)Trp-OH.

TLC: 0.43 (Rf2)
HPLC eluting time: 27.0 minutes

Mass analysis: $(M+H)^+ = 999.6$

Example 75. Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-Iqu-OH

Using Boc-Iqu-OH and H-(D)Trp-OCH_3 • HCl in place of Boc-Tyr-OH and H-(D)Phe-OBzl • HCl, respectively, in the production in Example 1, the same procedure as in Example 1 was followed to yield Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-Iqu-OCH_3, which was subjected to the same ester hydrolysis and purification procedures as in Example 43 to yield 27 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Tyr-Iqu-OH.

TLC:	0.38 (Rf2)
HPLC eluting time:	22.5 minutes
Mass analysis:	$(M+H)^+ = 882.4$

Example 76. Production of Cyclohexyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using cyclohexanecarbonyl chloride in place of adamantan-1-ylcarbonyl chloride in the production in Example 19, the same procedure as in Example 19 was followed to yield 40 mg of a white powder of cyclohexyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.19 (Rf2)
HPLC eluting time:	24.3 minutes
Mass analysis:	$(M+H)^+ = 880$

Example 77. Production of Cycloheptyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH

Using cycloheptanecarboxylic acid in place of 1,2,3,4-tetrahydro-2-naphthoic acid in the production in Example 63, the same procedure as in Example 63 was followed to yield 23 mg of a white powder of cycloheptyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

TLC:	0.20 (Rf2)
HPLC eluting time:	25.2 minutes
Mass analysis:	$(M+H)^+ = 894$

Example 78. Production of Boc-Leu-(D)Trp-(D)Ala-(D)Glu(Tyr-(D)Phe)-OCH_3

Using Boc-(D)Glu-OCH_3 in place of Boc-βAla-OH in the production in Example 1, the same procedure as in Example 1 was followed to yield 61 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-(D)Glu(Tyr-(D)Phe)-OCH_3.

TLC:	0.30 (Rf2)
HPLC eluting time:	24.8 minutes
Mass analysis:	$(M+H)^+ = 942.5$

Example 79. Production of Boc-Leu-(D)Trp-(D)Ala-(D)Glu(Tyr-(D)Phe)-OH

The compound of Example 78 was subjected to the same ester hydrolysis and purification procedures as in Example 43 to yield 21 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-(D)Glu(Tyr-(D)Phe)-OH.

TLC:	0.25 (Rf3)
HPLC eluting time:	23.7 minutes
Mass analysis:	$(M+H)^+ = 928.5$

Example 80

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 70, the same procedure as in Example 1 was followed to yield the following compounds 80-1 through 80-3.

80-1: Boc-Leu-(D)Trp-(D)Pya(2)-βAla-Tyr-Phe-OH

80-2: Boc-Leu-(D)Trp-(D)Pya(2)-βAla-(D)Tyr-(D)Phe-OH
80-3: Boc-Leu-(D)Trp-(D)Pya(2)-βAla-(D)Tyr-Phe-OH

Example 81

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 71, the same procedure as in Example 1 was followed to yield the following compounds 81-1 through 81-3.

81-1: Boc-Leu-(D)Trp-(D)Pya(3)-βAla-Tyr-Phe-OH
81-2: Boc-Leu-(D)Trp-(D)Pya(3)-βAla-(D)Tyr-(D)Phe-OH
81-3: Boc-Leu-(D)Trp-(D)Pya(3)-βAla-(D)Tyr-Phe-OH

Example 82

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 69, the same procedure as in Example 1 was followed to yield the following compounds 82-1 through 82-3.

82-1: Boc-Leu-(D)Trp(Me)-(D)Ala-βAla-Tyr-Phe-OH
82-2: Boc-Leu-(D)Trp(Me)-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
82-3: Boc-Leu-(D)Trp(Me)-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 83

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 57, the same procedure as Example 1 was followed to yield the following compounds 83-1 through 83-3.

83-1: 2-furyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
83-2: 2-furyl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
83-3: 2-furyl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 84

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production in Examples 58, the same procedure as in Example 19 was followed to yield the following compounds 84-1 through 84-3.

84-1: 2-thienyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
84-2: 2-thienyl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
84-3: 2-thienyl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 85

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production in Examples 59, the same procedure as in Example 19 was followed to yield the following compounds 85-1 through 85-3.

85-1: Quinoxalin-2-yl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
85-2: Quinoxalin-2-yl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
85-3: Quinoxalin-2-yl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 86

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production in Examples 60, the same procedur as in Example 19 was followed to yield the following compounds 86-1 through 86-3.

86-1: Ph-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
86-2: Ph-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
86-3: Ph-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 87

Using 10,11-Dihydro-5H-dibenz(b,f)azepine-5-carbonyl chloride in place of Adamantan-1-ylcarbonyl chloride in the production in Examples 19 and 20, the same procedure as in Example 19 was followed to yield the following compounds 87-1 and 87-2. Also, using Boc-(D)Tyr-OH in place of Boc-Tyr-OH in the production of compounds 87-1 and 87-2, the same procedure as in Example 19 was followed to yield the following compounds 87-3 and 87-4.

87-1: Dba-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH
87-2: Dba-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
87-3: Dba-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
87-4: Dba-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 88

Using the corresponding dipeptide of Examples 3 and 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 39, the same procedure as in Example 39 was followed to yield the following compounds 88-1 and 88-2.

88-1: Hexamethylenimino-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
88-2: Hexamethylenimino-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 89

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl and in the production of compounds 68, the same procedure as in Example 39 was followed to yield the following compounds 89-1 through 89-3.

89-1: Hexamethylenimino-CO-Leu-(D)Trp(Me)-Pya(2)-βAla-Tyr-Phe-OH
89-2: Hexamethylenimino-CO-Leu-(D)Trp(Me)-Pya(2)-βAla-(D)Tyr-(D)Phe-OH
89-3: Hexamethylenimino-CO-Leu-(D)Trp(Me)-Pya(2)-βAla-(D)Tyr-Phe-OH

Example 90

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 67, the same procedure as in Example 39 was followed to yield the following compounds 90-1 through 90-3.

90-1: Hexamethylenimino-CO-Leu-(D)Trp(Me)-(D)Ala-βAla-Tyr-Phe-OH
90-2: Hexamethylenimino-CO-Leu-(D)Trp(Me)-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
90-3: Hexamethylenimino-CO-Leu-(D)Trp(Me)-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 91

Using Boc-(D)Tyr-OBzl, Boc-Tyr-OBzl, Boc-(D)Phe-OBzl or Boc-Phe-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 62, the same procedure as in Example 62 was followed to yield the following compounds 91-1 through 91-4.

91-1: PhNH-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-OH
91-2: PhNH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-OH
91-3: PhNH-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Phe-OH
91-4: PhNH-CO-Leu-(D)Trp-(D)Ala-βAla-Phe-OH

Example 92

Using Boc-Glu(OBzl)-OPac, Boc-Glu(OPac)-OBzl, Boc-(D)Asp(OBzl)-OPac or Boc-(D)Asp(OPac)-OBzl in place of Boc-Tyr-(D)Phe-OBz in the production in compound 56, the same procedure as in Example 56 was followed to yield the following compounds 92-1 through 92-4.

92-1: $PhCH_2NH$-CO-Leu-(D)Trp-(D)Ala-βAla-Glu(OBzl)-OH
92-2: $PhCH_2NH$-CO-Leu-(D)Trp-(D)Ala-βAla-Glu-OBzl
92-3: $PhCH_2NH$-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Asp(OBzl)-OH
92-4: $PhCH_2NH$-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Asp-OBzl

Example 93

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 53, the same procedure as in Example 39 was followed to yield the following compounds 93-1 through 93-3.

93-1: $(Cyclohexyl)_2N$-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
93-2: $(Cyclohexyl)_2N$-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
93-3: $(Cyclohexyl)_2N$-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 94

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compounds 52, the same procedure as in Example 19 was followed to yield the following compounds 94-1 through 94-3.

94-1: Cyclohexyl-NH-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
94-2: Cyclohexyl-NH-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
94-3: Cyclohexyl-NH-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 95

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 61, the same procedure as in Example 19 was followed to yield the following compounds 95-1 through 95-3.

95-1: Ph_2N-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
95-2: Ph_2N-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
95-3: Ph_2N-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 96

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 64, the same procedure as in Example 1 was followed to yield the following compounds 96-1 through 96-3.

96-1: 2,2-dimethylbutyryl-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
96-2: 2,2-dimethylbutyryl-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
96-3: 2,2-dimethylbutyryl-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 97

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 76, the same procedure as in Example 19 was followed to yield the following compounds 97-1 through 97-3.

97-1: Cyclohexyl-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH

97-2: Cyclohexyl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
97-3: Cyclohexyl-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Example 98

Using the corresponding dipeptide of Examples 2 to 4 respectively in place of Boc-Tyr-(D)Phe-OBzl in the production of compound 63, the same procedure as in Example 63 was followed to yield the following compounds 98-1 through 98-3.

98-1: Tna-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-Phe-OH
98-2: Tna-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-(D)Phe-OH
98-3: Tna-CO-Leu-(D)Trp-(D)Ala-βAla-(D)Tyr-Phe-OH

Reference Example 1

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-OH

Using Boc-Glu(OBzl)-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 150 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-Glu-OH.

TLC (Rf2) 0.12, HPLC eluting time 20.9 minutes
Mass analysis: $(M+H)^+ = 689.6$

Reference Example 2

Production of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Leu-OH

Using Boc-(D)Leu-OBzl in place of Boc-Tyr-(D)Phe-OBzl in the production in Example 1, the same procedure as in Example 1 was followed to yield 134 mg of a white powder of Boc-Leu-(D)Trp-(D)Ala-βAla-(D)Leu-OH.

TLC (Rf2) 0.48, HPLC eluting time 24.0 minutes
Mass analysis: $(M+H)^+ = 673.3$

Test Example

Receptor binding assay

The membrane fraction prepared from swine heart was diluted to 0.15 mg/ml with an assaying buffer and dispensed to assaying tubes at 100 µl per tube. To this membrane fraction suspension were added 2 µl of a solution of endothelin-1 labeled with 5 nM radioactive iodine and 3 µl of a 50% dimethylsulfoxide solution of the subject peptide, followed by incubation at 25°C. After 1 hour, the suspension was diluted with 900 µl of an ice-cooled assaying buffer and centrifuged at 12,000 × G for 10 minutes to separate supernatant and precipitate. The precipitate contained cell membranes and endothelin receptors embedded therein. The receptor-bound endothelin, labeled with radioactive iodine, was also recovered in the precipitate. The radioactive iodine in this precipitate was counted, using a gamma ray counter, to determine the amount of radioactive-iodine-labeled endothelin bound to the endothelin receptors. The results of the quantitative determination are shown in IC_{50} (M) below.

Compound of Example 1	:4.6×10^{-9}
Compound of Example 2	:9.0×10^{-9}
Compound of Example 5	:7.2×10^{-9}
Compound of Example 38	:6.0×10^{-8}
Compound of Example 39	:3.4×10^{-10}
Compound of Example 43	:7.1×10^{-10}
Compound of Reference Example 1	:7.0×10^{-7}
Compound of Reference Example 2	:4.2×10^{-7}

The above result shows that peptides having an aromatic cycle of this invention have an more excellent endothelin receptor-antagonistic activity compared with peptides having no aromatic cycles.

Claims

1. A peptide represented by the formula:

$$R_1\text{-CO-}\overset{R_2}{\underset{}{N}}\text{-}\underset{(L)}{\overset{R_3}{CH}}\text{-CO-NH-}\underset{(D)}{\overset{R_4}{CH}}\text{-CO-}\overset{R_5}{N}\text{-}\overset{R_6}{CH}\text{-}(CH_2)_n\text{-CO-NH-}(CH_2)_m\text{-CO-X}$$

wherein R_1 represents

(i) a straight or branched C_1-C_{10} alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_3-C_8 cycloalkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_1-C_6 alkoxycarbonyl group, a C_6-C_{12} aromatic hydrocarbon group which may be substituted by a halogen atom, hydroxy group, C_1-C_3 alkoxy group or C_1-C_3 alkyl group and a 5- to 10-membered aromatic heterocyclic group,
(ii) a C_3-C_{10} cycloalkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_1-C_6 alkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group and a C_1-C_6 alkoxycarbonyl group, or the cycloalkyl group as condensed with a benzene ring,
(iii) a straight or branched C_1-C_8 alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group and a C_1-C_6 alkoxycarbonyl group,
(iv) a C_6-C_{15} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_6 alkoxycarbonyl group,
(v) a 5- to 6-membered aromatic heterocyclic group which contains 1 to 4 heteroatoms of O, S and N, or the group as condensed with a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_6 alkoxycarbonyl group, or
(vi) a group represented by R_7NH- or R_8R_9N-wherein R_7, R_8 and R_9 independently represent **(i)** a C_4-C_{10} alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_3-C_8 cycloalkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a hydroxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, a C_6-C_{12} aromatic hydrocarbon group which may be substituted by a halogen atom, a hydroxy group, a C_1-C_3 alkoxy group or a C_1-C_3 alkyl group, and a 5- to 10- membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, S and N, **(ii)** a C_5-C_{10} cycloalkyl group, which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a hydroxy group, a carboxyl group and a C_1-C_6 alkylcarbonyl group, **(iii)** a C_6-C_{12} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxy group, a carboxyl group and a C_1-C_6 alkylcarbonyl group, or **(iv)** a 5- to 10- membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, N and S or the group as condensed with a benzene ring wherein a carbon atom which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a hydroxyl group, a carboxyl group and a C_1-C_6 alkylcarbonyl group, and a nitrogen atom which may be substituted by 1 to 3 C_1-C_6 alkyl groups, and R_8 and R_9 may bind together to form a 5- to 13-membered nitrogen-containing heterocyclic ring which may have 1 or 2 hetero atoms such as an oxygen atom and a sulfur atom, the said 5- to 13-membered nitrogen-containing heterocyclic ring being optionally substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a phenyl group, a halogen atom, a nitro group, a cyano group, a hydroxy group, a C_1-C_4 alkoxy group, a C_1-C_4 alkylthio group, an amino group, a mono- or di-C_1-C_4 alkylamino group, a C_1-C_4 alkylcarbonylamino group, a C_1-C_4 alkylsulfonylamino group, a C_1-C_4 alkoxycarbonyl group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_4 alkylcarbonyloxy group and a 5- or 6-membered heterocyclic group having 1 to 4 hetero atoms such as O, S and N;

R_2 and R_5 independently represent a hydrogen atom or a straight or branched C_1-C_6 alkyl group;

R_3 is a C_1-C_8 alkyl, C_3-C_8 cycloalkyl or C_3-C_8 cycloalkyl-C_1-C_8 alkyl group wherein a methylene (-CH_2-) of the group may be interrupted by an oxygen atom or a sulfur atom;

R_4 is a heterocyclic-substituted C_1-C_6 alkyl group which may be substituted wherein the heterocycle is a 5- or 6-membered heterocyclic group having 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring, and the carbon atom of the heterocyclic-substituted C_1-C_6 alkyl group may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a hydroxyl group, a carboxyl group, a C_1-C_6 alkoxy group and a C_1-C_6 alkylcarbonyl group, and the nitrogen atom of the heterocyclic-substituted C_1-C_6 alkyl group may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkylcarbonyl group and a hydroxy-C_1-C_6 alkyl group;

R_6 represents a hydrogen atom, a straight or branched C_1-C_6 alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of (I) a C_6-C_{15} aromatic hydrocarbon group, (II) a 5-to 6-membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, S and N or the group as condensed with another aromatic ring, (III) a sulfur-containing group selected from the group consisting of a thione, mercapto, methylthio, ethylthio and phenylthio, (IV) a oxygen-containing group selected from the group consisting of a ketone, hydroxy, methoxy, ethoxy, phenoxy and benzyloxy group and (V) a nitrogen-containing group selected from the group consisting of an amino, N-methylamino, N-ethylamino and guanidino, a C_6-C_{12} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylcarbonyl group and a C_1-C_6 alkoxycarbonyl group, or a 5- or 6-membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a C_1-C_6 alkoxy group, a C_1-C_6 alkylthio group, a C_1-C_6 alkylcarbonyl group and a C_1-C_6 alkoxycarbonyl group;

X is (i) a group resulting from elimination of one hydrogen atom from the α-amino group of an α-amino acid having an aromatic cyclic group or (ii) an alkylamino group substituted by an aromatic cyclic group wherein the aromatic cyclic group is (i) a C_6-C_{15} aromatic hydrocarbon group which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group and a C_1-C_6 alkoxycarbonyl group, or (ii) a 5- or 6-membered aromatic heterocyclic group having 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a carboxyl group, a C_1-C_6 alkylcarbonyl group, and a C_1-C_6 alkoxycarbonyl group,

n represents 0 or an integer of 1 to 4 and

m represents an integer of 2 to 6 or a salt thereof.

2. The peptide as claimed in claim 1 wherein the 5- to 13-membered nitrogen-containing heterocyclic ring which may have 1 or 2 hetero atoms such as an oxygen atom and a sulfur atom forced by R_8 and R_9 is a pyrrolidinyl, piperidinyl, hexamethyleneiminyl, heptamethyleneiminyl, oxazolidinyl, morphonyl, thiazolidinyl, thiomorphonyl, imidazolidinyl, piperazinyl, pyrrolyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 2-oxazolidonyl, 2-thiazolidonyl, imidazolyl, 1,4,5,6-tetrahydropyrimidinyl, 2,3-dihydro-1H-indolyl, 1,2,3,4-tetrahydroquinolinyl, 2,3,4,5-tetrahydro1H-1-benzazepinyl, 2,3-dihydro-1H-isoindolyl, 1,2,3,4-tetrahydroisoquinolyl, 2,3,4,5-tetrahydro-1H-2-benzazepinyl, 2,3,4,5-tetrahydro-1H-3-benzazepinyl, 1,2,3,4,5,6-hexahydro-1-benzazocinyl, 1,2,3,4,5,6-hexahydro-2-benzazocinyl, 1,2,3,4,5,6-hexahydro-3-benzazocinyl, 2,3,4,5,6,7-hexahydro-1H-1-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-2-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-3-benzazonyl, 2,3,4,5,6,7-hexahydro-1H-4-benzazonyl, β-carbolynyl, phenothiadinyl, 3H-3-benzazepinyl, 3,4-dihydroquinolyl, benzimidanyl, 1,4-benzodiazepinyl or 10,11-dihydro-5H-dibenz(b,f)azepine-5-yl.

3. The peptide as claimed in claim 1 wherein the ring formed by R_8 and R_9 is a hexamethyleneiminyl, 10,11-dihydro-5H-dibenz(b,f)azepin-5-yl, morpholinyl, piperidinyl, methylpiperazinyl or 1-(2-pyrimidyl)piperazinyl.

4. The peptide as claimed in claim 1 wherein the C_6-C_{15} aromatic hydrocarbon group of R_1 is a phenyl or naphthyl group.

5. The peptide as claimed in claim 1 wherein the 5- or 6-membered heterocyclic group which contains 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring of R_1 is a 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, thiazol-4-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyranyl, indol-3-yl, N-methylindol-3-yl, 2-quinolyl or quinoxalin-2-yl group.

6. The peptide as claimed in claim 1 wherein R_1 is a straight or branched C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxy, phenyl, naphthyl, phenyl-C_1-C_{10} alkyl, indan-1-yl, indan-2-yl, 1,2,3,4-tetrahydronaphthalene-1-yl, 1,2,3,4-tetrahydronaphthalene-2-yl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, thiazol-4-yl, 2-pyridyl, 4-pyridyl, 2-pyranyl, indol-3-yl, N-methylindol-3-yl, 2-quinolyl, quinoxalin-2-yl, mono- or di-phenylamino, phenyl-C_1-C_{10} alkyl amino, methylpiperazino or 1-(2-pyrimidyl)piperazino.

7. The peptide as claimed in claim 1 wherein R_2 is a hydrogen atom.

8. The peptide as claimed in claim 1 wherein the C_1-C_8 alkyl group wherein a methylene ($-CH_2-$) of the group interrupted by an oxygen atom or a sulfur atom of R_3 is a methoxymethyl, ethoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, methylthiomethyl, ethylthiomethyl, 2-methylthioethyl, 2-ethylthioethyl, 3-methylthiopropyl or 3-ethylthiopropyl group.

9. The peptide as claimed in claim 1 wherein the C_3-C_8 cycloalkyl group wherein a methylene ($-CH_2-$) of the group interrupted by an oxygen atom or a sulfur atom is a tetrahydrofuran-2-yl or tetrahydrothiophen-2-yl group.

10. The peptide as claimed in claim 1 wherein the C_3-C_8 cycloalkyl-C_1-C_8 alkyl group wherein a methylene ($-CH_2-$) of the group interrupted by an oxygen atom or a sulfur atom is a cyclopentylthiomethyl or cyclohexylthiomethyl group.

11. The peptide as claimed in claim 1 wherein R_3 is a C_1-C_6 alkyl group.

12. The peptide as claimed in claim 1 wherein R_4 is a 2-pyridyl-C_1-C_6 alkyl, imidazol-2-yl-C_1-C_6 alkyl, imidazol-4-yl-C_1-C_6 alkyl, indol-3-yl-C_1-C_6 alkyl, N-methylindol-3-yl-C_1-C_6 alkyl, N-ethylindol-3-yl-C_1-C_6 alkyl, N-hydroxymethylindol-3-yl-C_1-C_6 alkyl, N-formylindol-3-yl-C_1-C_6 alkyl, thiazol-4-yl-C_1-C_6 alkyl or 5-fluoroindol-3-yl-C_1-C_6 alkyl group.

13. The peptide as claimed in claim 1 wherein R_4 is a indol-3-yl-C_1-C_6 alkyl or N-methylindol-3-yl-C_1-C_6 alkyl group.

14. The peptide as claimed in claim 1 wherein R_5 is a hydrogen atom.

15. The peptide as claimed in claim 1 wherein the C_6-C_{12} aromatic hydrocarbon group of R_6 is a phenyl, 1-naphthyl or 2-naphthyl group.

16. The peptide as claimed in claim 1 wherein the 5- or 6-membered aromatic heterocyclic group which contains 1 to 4 hetero atoms of O, S and N or the group as condensed with a benzene ring of R_6 is a furyl, thienyl, pyridyl, thiazolyl, imidazolyl or indolyl group.

17. The peptide as claimed in claim 1 wherein R_6 is a C_1-C_6 alkyl, furyl, thienyl, pyridyl, pyridyl-C_1-C_6 alkyl or indolyl-C_1-C_6 alkyl group.

18. The peptide as claimed in claim 1 wherein the C_6-C_{15} aromatic hydrocarbon group of X is a phenyl or α-naphthyl group.

19. The peptide as claimed in claim 1 wherein the 5- or 6-membered aromatic heterocyclic group having 1 to 4 hetero atoms of O, S and N or the group condensed with benzene rings of X is a 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, thiazol-4-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyranyl, indol-3-yl, N-methylindol-3-yl, 2-quinolyl or quinoxalin-2-yl group.

20. The peptide as claimed in claim 1 wherein the α-amino acid of X may be substituted or protected at a 1-carboxyl group thereof by an ester or an amide group.

21. The peptide as claimed in claim 1 wherein the α-amino acid of X is Gly, Ala, Val, Leu, Ile, Ser, Thr, Glu, Asn, Phe, Trp, Met, His, Cys, Arg, Asn, Gln, Tyr, (I)Tyr, diiodo-Tyr, Phg, Cha, Nva, Nle, Pya(2), Pya(3) or Thi which may be substituted or protected at a 1-carboxyl group thereof by (i) an ester selected from the group consisting of a benzyl ester, diphenylmethyl ester and trityl ester or (ii) an amide selected from the group consisting of a phenylamide, benzylamide, diphenylamide, dibenzylamide, 2-phenylethylamide, 2,2-diphenylethylamide, 1,2-diphenylethylamide and indol-3-yl-methylamide.

22. The peptide as claimed in claim 1 wherein the group resulting from elimination of one hydrogen atom from the α-amino group of an α-amino acid having an aromatic cyclic group of X is a group selected from the group consisting

of

Phe-OH, -Tyr-OH, -Trp-OH, -Phg-OH, -(m-F)Tyr-OH, -(p-F)Phe-OH, -(p-Cl)Phe-OH, -(p-Me)Phe-OH, -Trp(Me)-OH, - Trp(CHO)-OH, -Phe-Trp-OH, -Trp-Phe-OH,-Tyr-Trp-OH, -Trp-Phe-OH, -(m-F)Tyr-(p-F)Phe-OH, -Glu(OBzl)-OH, -Glu-OBzl, - Asp(OBzl)-OH, -Asp-OBzl, -Asp-Asp(OBzl)-OH, -Glu(NBzl$_2$)-OH, -Glu(NHBzl)-OH, -Asp(NBzl$_2$)-OH, -Asp(NHBzl)-OH, -Glu-NBzl$_2$, -Glu-NHBzl, -Asp-NBzl$_2$, -Asp-NHBzl, -Glu-NHCHPhCH$_2$Ph, -Asp-NHCHPhCH$_2$Ph, -Glu-NHCH$_2$CHPh$_2$, -Asp-NHCH$_2$CHPh$_2$, -Glu(NHCHPhCH$_2$Ph)-OH, -Asp(NHCHPhCH$_2$Ph)-OH -Glu(NHCH$_2$CHPh$_2$)-OH, -Asp(NHCH$_2$CHPh$_2$)-OH, -Glu(NHCH$_2$CH$_2$-Ind)-OH, -Asp(NHCH$_2$CH$_2$-Ind)-OH, -Glu-NHCH$_2$CH$_2$-Ind, -Asp-NHCH$_2$CH$_2$-Ind, -Trp-NH-Ind(OH), -Tyr-Iqu(OH), -(I)Tyr-Phe-OH, -Trp-Trp-OH, -Tyr(Bzl)-Phe-OH, -Tyr(Bzl)-Trp-OH, -(I)Tyr-Trp-OH, -(I)Tyr-Tyr-OH, -Trp-His-OH, -His-Trp-OH, -Tyr-His-OH, -His-Tyr-OH, -Phe-His-OH, -His-Phe-OH, -Phe-Trp-OH, -Phe-Tyr-OH and -Phe-Phe-OH.

23. The peptide as claimed in claim 1 wherein the alkylamino group of X is a C_1-C_{10} alkyl amino group or a C_3-C_{10} cycloalkyl amino group.

24. The peptide as claimed in claim 1 wherein the alkylamino group substituted by an aromatic cyclic group of X is a group selected from the group consisting of -NBzl$_2$, -NHBzl, -NHCHPhCH$_2$Ph, -NHCH$_2$CHPh$_2$ and -NHCH$_2$CH$_2$-Ind.

25. The peptide as claimed in claim 1 wherein X is a group selected from the group consisting of -Tyr-OH, -Phe-OH, -Trp-OH, -Phg-OH, Tyr-Phe-OH, -Tyr-Trp-OH, -Trp-Trp-OH, -(m-F)Tyr-OH, -(P-F)Phe-OH, -(m-F)Tyr-(p-F)Phe-OH, -(I)Tyr-Phe-OH, -Tyr(Bzl)-Phe-OH, -Trp(Bzl)-Trp-OH, -(I)Tyr-Trp-OH, -(I)Tyr-Tyr-OH, -Glu(Obzl)-OH, -Glu-OBzl, -Asp(OBzl)-OH, -Asp-Obzl, -Glu-NHCHPhCH$_2$Ph, -Glu-NHCH$_2$CHPh$_2$, -Asp-NHCHPhCH$_2$Ph, -Asp-NHCH$_2$CHPh$_2$, -Asp-NHCH$_2$CH$_2$-Ind, Asp-(NHCH$_2$CH$_2$-Ind)-OH, Glu-Asp-NHCH$_2$CH$_2$-Ind, -Glu-Asp(NHCH$_2$CH$_2$-Ind)-NBzl$_2$, -Asp-NBzl$_2$, -Trp-NH-Ind and -Trp-Iqu.

26. The peptide as claimed in claim 1 wherein n is 0.

27. The peptide as claimed in claim 1 wherein n is 0 and the -N(R$_5$)(HCR$_6$)-(CH$_2$)$_n$-CO moiety is an α-amino acid residue selected from the group consisting of Ala, Val, Leu, Ile, Trp, Pya(2) and Pya(3).

28. The peptide as claimed in claim 1 wherein n is 2, 3 or 5.

29. The peptide as claimed in claim 1 wherein R_1 is a hexamethyleneimino group, R_2 is a hydrogen atom, R_3 is a C_{1-6} alkyl group, R_4 is a indol-3-yl-C_{1-6} alkyl group, R_5 is a hydrogen atom, R_6 is a C_{1-6} alkyl group or a 5- or 6-membered aromatic heterocyclic group having 1 to 4 hetero atoms of O, S and N, m is 2, n is 0 and X is -Tyr-(D)Phe-OH, -Tyr(I)-(D)Phe-OH or -Trp-NH-Ind-OH.

30. The peptide as claimed in claim 1 wherein R_1 is a hexamethyleneimino group, R_2 is a hydrogen atom, R_3 is a C_{1-6} alkyl group, R_4 is a indol-3-yl-C_{1-6} alkyl group, R_5 is a hydrogen atom, R_6 is a C_{1-6} alkyl group, m is 2, n is 0 and X is -Tyr-(D)Phe-OH.

31. Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH, or a pharmaceutically acceptable salt thereof.

32. Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr(I)-(D)Phe-OH, or a pharmaceutically acceptable salt thereof.

33. Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OH, or a pharmaceutically acceptable salt thereof.

34. Hexamethyleneimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

35. A method of producing the peptide of claim 1 wherein a partial peptide or amino acids capable of constituting the peptide represented by the formula of claim 1 are condensed with the remaining moiety, and when the product has a protected group, it is deprotected.

36. A pharmaceutical composition containing the peptide of one of claims 1 to 34 or a pharmacologically acceptable salt thereof.

37. The pharmaceutical composition of claim 36 which is an endothelin receptor antagonist.

38. Use of the peptide or a pharmaceutically acceptable salt therof as claimed in one of claims 1 to 34 for preparing an endothelin receptor antagonist.

Patentansprüche

1. Peptid der Formel

$$R_1\text{-CO-}\overset{R_2}{\overset{|}{N}}\text{-}\underset{(L)}{\overset{R_3}{\overset{|}{CH}}}\text{-CO-NH-}\underset{(D)}{\overset{R_4}{\overset{|}{CH}}}\text{-CO-}\overset{R_5}{\overset{|}{N}}\text{-}\overset{R_6}{\overset{|}{CH}}\text{-}(CH_2)n\text{-CO-NH-}(CH_2)m\text{-CO-X}$$

worin R_1

(i) eine gerade oder verzweigte C_1-C_{10}-Alkylgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_3-C_8-Cycloalkylgruppe, einem Halogenatom, einer C_1-C_6-Alkoxygruppe, einer C_1-C_6-Alkylthiogruppe, einer C_1-C_6-Alxoxycarbonylgruppe, einer aromatischen C_6-C_{12}-Kohlenwasserstoffgruppe, die mit einem Halogenatom, einer Hydroxygruppe, einer C_1-C_3-Alkoxygruppe oder einer C_1-C_3-Alkylgruppe substituiert sein kann, und einer 5- bis 10-gliedrigen aromatischen heterocydischen Gruppe substituiert sein kann,
(ii) eine C_3-C_{10}-Cycloalkylgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer C_1-C_6-Alkoxygruppe, einer C_1-C_6-Alkylthiogruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann, oder diese Cycloalkylgruppe kondensiert mit einem Benzolring,
(iii) eine gerade oder verzweigte C_1-C_8-Alkoxygruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_3-C_8-Cycloalkylgruppe, einer C_1-C_6-Alkoxygruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann,
(iv) eine aromatische C_6-C_{15}-Kohlenwasserstoffgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einem Halogenatom, einer Hydroxygruppe, einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einer Carboxylgruppe, einer C_1-C_6-Alkylcarbonylgruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann,
(v) eine 5- bis 6-gliedrige aromatische heterocydische Gruppe, die ein bis vier Heteroatome ausgewählt aus O, S und N enthält oder diese Gruppe kondensiert mit einem Benzolring, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einem Halogenatom, einer Hydroxygruppe, einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einer Carboxylgruppe, einer C_1-C_6-Alkylcarbonylgruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann oder
(vi) eine Gruppe R_7NH- oder R_8R_9N- bedeutet, worin R_7, R_8 und R_9 unabhängig (i) eine C_4-C_{10}-Alkylgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_3-C_8-Cycloalkylgruppe, einer C_1-C_6-Alkoxygruppe, einer C_1-C_6-Alkylthiogruppe, einer Hydroxygruppe, einer Carboxylgruppe, einer C_1-C_6-Alkylcarbonylgruppe, einer aromatischen C_6-C_{12}-Kohlenwasserstoffgruppe, die mit einem Halogenatom, einer Hydroxygruppe, einer C_1-C_3-Alkoxygruppe oder einer C_1-C_3-Alkylgruppe substituiert sein kann, und einer 5- bis 10-gliedrigen aromatischen heterocydischen Gruppe, die 1 bis 4 Heteroatome ausgewählt aus O, S und N enthält, substituiert sein kann, (ii) eine C_5-C_{10}-Cycloalkylgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einer C_1-C_6-Alkylthiogruppe, einer Hydroxygruppe, einer Carboxylgruppe und einer C_1-C_6-Alkylcarbonylgruppe substituiert sein kann, (iii) eine aromatische C_6-C_{12}-Kohlenwasserstoffgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einer Hydroxygruppe, einer Carboxylgruppe und einer C_1-C_6-Alkylcarbonylgruppe substituiert sein kann oder (iv) eine 5- bis 10-gliedrige aromatische heterocydische Gruppe, die 1 bis 4 Heteroatome ausgewählt aus O, N und S enthält, oder diese Gruppe komdensiert mit einem Benzolring bedeuten, worin ein Kohlenstoffatom, das mit 1 bis 3 Substituenten

ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einer Hydroxylgruppe, einer Carboxylgruppe und einer C_1-C_6-Alkylcarbonylgruppe substituiert sein kann, und ein Stickstoffatom, das mit 1 bis 3 C_1-C_6-Alkylgruppen substituiert sein kann, und R_8 und R_9 miteinander verbunden sein können unter Bildung eines 5- bis 13-gliedrigen stickstoffhaltigen heterocyclischen Rings, der ein oder zwei Heteroatome aufweisen kann, wie ein Sauerstoffatom und ein Schwefelatom, wobei der 5-bis 13-gliedrige stickstoffhaltige heterocyclische Ring gegebenenfalls mit 1 bis 3 Substituenten substituiert ist, ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einer Phenylgruppe, einem Halogenatom, einer Nitrogruppe, einer Cyanogruppe, einer Hydroxygruppe, einer C_1-C_4-Alkoxygruppe, einer C_1-C_4-Alkylthiogruppe, einer Aminogruppe, einer Mono- oder Di-C_1-C_4-Alkylaminogruppe, einer C_1-C_4-Alkylcarbonylaminogruppe, einer C_1-C_4-Alkylsulfonylaminogruppe, einer C_1-C_4-Alkoxycarbonylgruppe, einer Carboxylgruppe, einer C_1-C_6-Alkylcarbonylgruppe und einer C_1-C_4-Alkylcarbonyloxygruppe, und einer 5- oder 6-glied-rigen heterocyclischen Gruppe mit 1 bis 4 Heteroatomen wie O, S und N;

R_2 und R_4 unabhängig ein Wasserstoffatom oder eine gerade oder verzweigte C_1-C_6-Alkylgruppe bedeuten;
R_3 eine C_1-C_8-Alkyl-, C_3-C_8-Cycloalkyl- oder C_3-C_8-Cycloalkyl-C_1-C_8-Alkylgruppe ist, worin ein Methylenrest (-CH_2-) der Gruppe durch ein Sauerstoffatom oder ein Schwefelatom unterbrochen sein kann;
R_4 eine heterocyclisch substituierte C_1-C_6-Alkylgruppe, die substituiert sein kann, worin der Heterocyclus eine 5- oder 6-gliedrige heterocyclische Gruppe mit 1 bis 4 Heteroatomen ausgewählt aus O, S und N ist oder diese Gruppe kondensiert mit einem Benzolring ist, wobei das Kohlenstoffatom der heterocyclisch substituierten C_1-C_6-Alkylgruppe mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer Hydroxylgruppe, einer Carboxylgruppe, einer C_1-C_6-Alkoxygruppe und einer C_1-C_6-Alkylcarbonylgruppe substituiert sein kann, und das Stickstoffatom der heterocyclisch substituierten C_1-C_6-Alkylgruppe mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkylcarbonylgruppe und einer Hydroxy-C_1-C_6Alkylgruppe substituiert sein kann;
R_6 ein Wasserstoffatom, eine gerade oder verzweigte C_1-C_6-Alkylgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus (i) einer aromatischen C_6-C_{15}-Kohlenwasserstoffgruppe, (ii) einer 5- bis 6-gliedrigen aromatischen heterocyclischen Gruppe, die 1 bis 4 Heteroatome ausgewählt aus O, S und N enthält, oder diese Gruppe kondensiert mit einem weiteren aromatischen Ring, (iii) einer schwefelhaltigen Gruppe ausgewählt aus der Gruppe bestehend aus einer Thion-, Mercapto-, Methylthio-, Ethylthio- und Phenylthiogruppe, (iv) einer sauerstoffhaltigen Gruppe ausgewählt aus der Gruppe bestehend aus einer Keton-, Hydroxy-, Methoxy-, Ethoxy-, Phenoxy- und Benzyloxygruppe und (v) einer stickstoffhaltigen Gruppe ausgewählt aus der Gruppe bestehend aus einer Amino-, N-Methylamino-, N-Ethylamino- und Guanidinogruppe substituiert sein kann, eine aromatische C_6-C_{12}-Kohlenwasserstoffgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer C_1-C_6-Alkoxygruppe, einer C_1-C_6-Alkylthiogruppe, einer C_1-C_6-Alkylcarbonylgruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann, oder eine 5- oder 6-gliedrige aromatische heterocyclische Gruppe, die 1 bis 4 Heteroatome ausgewählt aus O, S und N enthält, oder diese Gruppe kondensiert mit einem Benzolring, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einer C_1-C_6-Alkylgruppe, einem Halogenatom, einer C_1-C_6-Alkoxygruppe, einer C_1-C_6-Alkylthiogruppe, einer: C_1-C_6-Alkylcarbonylgruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann, bedeutet;
X (i) eine Gruppe ist, die durch Eliminierung eines Wasserstoffatoms der α-Aminogruppe einer α-Aminosäure mit einer aromatischen cyclischen Gruppe entsteht oder (ii) eine Alkylaminogruppe ist, die mit einer aromatischen cyclischen Gruppe substituiert ist, worin die aromatische cyclische Gruppe (i) eine aromatische C_6-C_{15}-Kohlenwasserstoffgruppe, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einem Halogenatom, einer Hydroxygruppe, einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einer Carboxylgruppe, einer C_1-C_6-Alkylcarbonylgruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann oder (ii) eine 5- oder 6-gliedrige aromatische heterocyclische Gruppe mit 1 bis 4 Heteroatomen ausgewählt aus O, S und N oder die Gruppe kondensiert mit einem Benzolring ist, die mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus einem Halogenatom, einer Hydroxygruppe, einer C_1-C_6-Alkylgruppe, einer C_1-C_6-Alkoxygruppe, einer carboxylgruppe, einer C_1-C_6-Alkylcarbonylgruppe und einer C_1-C_6-Alkoxycarbonylgruppe substituiert sein kann,
n 0 oder eine ganze Zahl von 1 bis 4 bedeutet und
m eine ganze Zahl von 2 bis 6 bedeutet,
oder ein Salz davon.

2. Peptid nach Anspruch 1, worin der 5- bis 13-gliedrige stickstoffhaltige heterocyclische Ring, der 1 oder 2 Heteroatome, wie ein Sauerstoffatom und ein Schwefelatom aufweisen kann, der durch R_8 und R_9 gebildet wird, ein Pyrrolidinyl-, Piperidinyl-, Hexamethyleniminyl-, Heptamethyleniminyl-, Oxazolidinyl-, Morphonyl-, Thiazolidinyl-,

Thiomorphonyl-, Imidazolidinyl-, Piperazinyl-, Pyrrolyl-, 1,2-Dihydropyridinyl-, 1,4-Dihydropyridinyl-, 1,2,3,6-Tetrahydropyridinyl-, 2-Oxazolidonyl-, 2-Thiazolidonyl-, Imidazolyl-, 1,4,5,6-Tetrahydropyrimidinyl-, 2-3-Dihydro-1H-indolyl-, 1,2,3,4-Tetrahydrochinolinyl-, 2,3,4,5-Tetrahydro-1H-1-benzazepinyl-, 2,3-Dihydro-1H-isoindolyl-, 1,2,3,4-Tetrahydroisochinolyl-, 2,3,4,5-Tetrahydro-1H-2-benzazepinyl-, 2,3,4,5-Tetrahydro-1H-3-benzazepinyl-, 1,2,3,4,5,6-Hexahydro-1-benzazocinyl-, 1,2,3,4,5,6-Hexahydro-2-benzazocinyl-, 1,2,3,4,5,6-Hexahydro-3-benzazocinyl-, 2,3,4,5,6,7-Hexahydro-1H-1-benzazonyl-, 2,3,4,5,6,7-Hexahydro-1H-2-benzazonyl-, 2,3,4,5,6,7-Hexahydro-1H-3-benzazonyl-, 2,3,4,5,6,7-Hexahydro-1H-4-Benzazonyl-, β-Carbolynyl-, Phenothiadinyl-, 3H-3-Benzazepinyl-, 3,4-Dihydrochinolyl-, Benzimidanyl-, 1,4-Benzodiazepinyl- oder 10,11-Dihydro-5H-dibenz(b,f)azepin-5-yl-Rest ist.

3. Peptid nach Anspruch 1, worin der durch R_8 und R_9 gebildete Ring ein Hexamethyleniminyl-, 10,11-Dihydro-5H-dibenz(b,f)azepin-5-yl-, Morpholinyl-, Piperidinyl-, Methylpiperazinyl- oder 1-(2-Pyrimidyl)piperazinylring ist.

4. Peptid nach Anspruch 1, worin die aromatische C_6-C_{15}-Kohlenwasserstoffgruppe von R_1 eine Phenyl- oder Naphthylgruppe ist.

5. Peptid nach Anspruch 1, worin die 5- oder 6-gliedrige heterocyclische Gruppe von R_1, die 1 bis 4 Heteroatome ausgewählt aus O, S und N enthält, oder die Gruppe, die mit einem Benzolring kondensiert ist, eine 2-Furyl-, 3-Furyl-, 2-Thienyl-, 3-Thienyl-, Thiazol-4-yl-, 2-Pyridyl-, 3-Pyridyl-, 4-Pyridyl-, 2-Pyranyl-, Indol-3-yl-, N-Methylindol-3-yl-, 2-Chinolyl- oder Chinoxalin-2-yl-Gruppe ist.

6. Peptid nach Anspruch 1, worin R_1 eine gerade oder verzweigte C_1-C_{10}-Alkyl-, C_3-C_8-cycloalkyl-, C_1-C_8-Alkoxy-, Phenyl-, Naphthyl-, Phenyl-C_1-C_{10}-alkyl-, Indan-1-yl-, Indan-2-yl-, 1,2,3,4-Tetrahydronaphthalin-1-yl-, 1,2,3,4-Tetrahydronaphthalin-2-yl-, 2-Furyl-, 3-Furyl-, 2-Thienyl-, 3-Thienyl-, Thiazol-4-yl-, 2-Pyridyl-, 4-Pyridyl-, 2-Pyranyl-, Indol-3-yl-, N-Methylindol-3-yl-, 2-Chinolyl-, Chinoxalin-2-yl-, Mono- oder Di-phenylamino-, Phenyl-C_1-C_{10}-alkylamino-, Methylpiperazino- oder 1-(2-Pyrimidyl)piperazinogruppe ist.

7. Peptid nach Anspruch 1, worin R_2 ein Wasserstoffatom ist.

8. Peptid nach Anspruch 1, worin die C_1-C_8-Alkylgruppe von R_3, bei der ein Methylenrest (-CH_2-) der Gruppe durch ein Sauerstoffatom oder ein Schwefelatom unterbrochen ist, eine Methoxymethyl-, Ethoxymethyl-, 2-Methoxyethyl-, 2-Ethoxyethyl-, 3-Methoxypropyl-, 3-Ethoxypropyl-, Methylthiomethyl-, Ethylthiomethyl-, 2-Methylthioethyl-, 2-Ethylthioethyl-, 3-Methylthiopropyl- oder 3-Ethylthiopropylgruppe ist.

9. Peptid nach Anspruch 1, worin die C_3-C_8-Cycloalkylgruppe, worin ein Methylenrest (-CH_2-) der Gruppe durch ein Sauerstoffatom oder ein Schwefelatom unterbrochen ist, eine Tetrahydrofuran-2-yl- oder Tetrahydrothiophen-2-ylgruppe ist.

10. Peptid nach Anspruch 1, worin die C_3-C_8-CycloalkylC_1-C_8-alkylgruppe, worin ein Methylenrest (-CH_2-) der Gruppe durch ein Sauerstoffatom oder ein Schwefelatom unterbrochen ist, eine Cyclopentylthiomethyl- oder Cyclohexylthiomethylgruppe ist.

11. Peptid nach Anspruch 1, worin R_3 eine C_1-C_6-Alkylgruppe ist.

12. Peptid nach Anspruch 1, worin R_4 eine 2-Pyridyl-C_1-C_6-alkyl-, Imidazol-2-yl-C_1-C_6-alkyl-, Imidazol-4-yl-C_1-C_6-alkyl-, Indol-3-yl-C_1-C_6-alkyl-, N-Methylindol-3-yl-C_1-C_6-alkyl-, N-Ethylindol-3-yl-C_1-C_6-alkyl-, N-Hydroxymethylindol-3-yl-C_1-C_6-alkyl-, N-Formyl-indol-3-yl-C_1-C_6-alkyl-, Thiazol-4-yl-C_1-C_6-alkyl- oder 5-Fluorindol-3-yl-C_1-C_6-alkylgruppe ist.

13. Peptid nach Anspruch 1, worin R_4 eine Indol-3-yl-C_1-C_6-alkyl- oder N-Methylindol-3-yl-C_1-C_6-alkylgruppe ist.

14. Peptid nach Anspruch 1, worin R_5 ein Wasserstoffatom ist.

15. Peptid nach Anspruch 1, worin die aromatische C_6-C_{12}-Kohlenwasserstoffgruppe von R_6 eine Phenyl-, 1-Naphthyl- oder 2-Naphthylgruppe ist.

16. Peptid nach Anspruch 1, worin die 5- oder 6-gliedrige aromatische heterocyclische Gruppe von R_6, die 1 bis 4 Heteroatome ausgewählt aus O, S und N enthält, oder die Gruppe, die mit einem Benzolring kondensiert ist, eine

Furyl-, Thienyl-, Pyridyl-, Thiazolyl-, Imidazolyl- oder Indolylgruppe ist.

17. Peptid nach Anspruch 1, worin R_6 eine C_1-C_6-Alkyl-, Furyl-, Thienyl-, Pyridyl-, Pyridyl-C_1-C_6-alkyl- oder Indolyl-C_1-C_6-alkylgruppe ist.

18. Peptid nach Anspruch 1, worin die aromatische C_6-C_{15}-Kohlenwasserstoffgruppe von X eine Phenyl- oder α-Naphthylgruppe ist.

19. Peptid nach Anspruch 1, worin die 5- oder 6-gliedrige aromatische heterocyclische Gruppe mit 1 bis 4 Heteroatomen ausgewählt aus O, S und N, oder die Gruppe, die mit Benzolringen kondensiert ist, von X eine 2-Furyl-, 3-Furyl-, 2-Thienyl-, 3-Thienyl-, Thiazol-4-yl-, 2-Pyridyl-, 3-Pyridyl-, 4-Pyridyl-, 2-Pyranyl-, Indol-3-yl-, N-Methylindol-3-yl-, 2-Chinolyl- oder Chinoxalin-2-ylgruppe ist.

20. Peptid nach Anspruch 1, worin die α-Aminosäure von X an einer 1-Carboxylgruppe durch eine Ester- oder Amidgruppe substituiert oder geschützt sein kann.

21. Peptid nach Anspruch 1, worin die α-Aminosäure von X Gly, Ala, Val, Leu, Ile, Ser, Thr, Glu, Asn, Phe, Trp, Met, His, Cys, Arg, Asn, Gln, Tyr, (I)Tyr, Diiod-Tyr, Phg, Cha, Nva, Nle, Pya(2), Pya(3) oder Thi ist, die an der 1-Carboxylgruppe mit (i) einem Ester ausgewählt aus der Gruppe bestehend aus einem Benzylester, Diphenylmethylester und Tritylester oder (ii) einem Amid ausgewählt aus der Gruppe bestehend aus Phenylamid, Benzylamid, Diphenylamid, Dibenzylamid, 2-Phenylethylamid, 2,2-Diphenylethylamid,1,2-Diphenylethylamid und Indol-3-ylmethylamid substituiert oder geschützt sein kann.

22. Peptid nach Anspruch 1, worin die Gruppe von X, die durch Eliminierung eines Wasserstoffatoms aus der α-Aminogruppe einer α-Aminosäure mit einer aromatischen cyclischen Gruppe entsteht, eine Gruppe ist ausgewählt aus der Gruppe bestehend aus Phe-OH, -Tyr-OH, -Trp-OH, -Phg-OH, -(m-F)Tyr-OH, -(p-F)Phe-OH, -(p-Cl)Phe-OH, -(p-Me)Phe-OH, -Trp(Me)-OH, -Trp(CHO)-OH, -Phe-Trp-OH, -Trp-Phe-OH, -Tyr-Trp-OH, -Trp-Phe-OH, -(m-F)Tyr-(p-F)Phe-OH, -Glu(OBzl)-OH, -Glu-OBzl, -Asp(OBzl)-OH, -Asp-OBzl, -Asp-Asp(OBzl)-OH, -Glu($NBzl_2$)-OH, -Glu(NHBzl)-OH, -Asp($NBzl_2$)-OH, -Asp(NHBzl)-OH, -Glu-$NBzl_2$, -Glu-NHBzl, -Asp-$NBzl_2$, -Asp-NHBzl, -Glu-$NHCHPhCH_2Ph$, -Asp-$NHCHPhCH_2Ph$, -Glu-$NHCH_2CHPh_2$, -Asp-$NHCH_2CHPh_2$, -Glu($NHCHPhCH_2Ph$)-OH, -Asp($NHCHPhCH_2Ph$)-OH, -Glu($NHCH_2CHPh_2$)-OH, -Asp($NHCH_2CHPh_2$)-OH, -Glu($NHCH_2CH_2$-Ind)-OH, -Asp($NHCH_2CH_2$-Ind)-OH, -Glu-$NHCH_2CH_2$-Ind, -Asp-$NHCH_2CH_2$-Ind, -Trp-NH-Ind(OH), -Tyr-Iqu(OH), (I)Tyr-Phe-OH, -Trp-Trp-OH, -Tyr(Bzl)-Phe-OH, -Tyr(Bzl)-Trp-OH, -(I)Tyr-Trp-OH, -(I)Tyr-Tyr-OH, -Trp-His-OH, -His-Trp-OH, -Tyr-His-OH, -His-Tyr-OH, -Phe-His-OH, -His-Phe-OH, -Phe-Trp-OH, -Phe-Tyr-OH, und -Phe-Phe-OH.

23. Peptid nach Anspruch 1, worin die Alkylaminogruppe von X eine C_1-C_{10}-Alkylaminogruppe oder eine C_3-C_{10}-Cycloalkylaminogruppe ist.

24. Peptid nach Anspruch 1, worin die Alkylaminogruppe von X, die mit einer aromatischen cyclischen Gruppe substituiert ist, eine Gruppe ist ausgewählt aus der Gruppe bestehend aus -$NBzl_2$, -NHBzl, -$NHCHPhCH_2Ph$, -$NHCH_2CHPh_2$ und -$NHCH_2CH_2$-Ind.

25. Peptid nach Anspruch 1, worin X eine Gruppe ist ausgewählt aus der Gruppe bestehend aus -Tyr-OH, -Phe-OH, -Trp-OH, -Phg-OH, -Tyr-Phe-OH, -Tyr-Trp-OH, -Trp-Trp-OH, -(m-F)Tyr-OH, -(p-F)Phe-OH, -(m-F)Tyr-(p-F)Phe-OH, -(I)Tyr-Phe-OH, -Tyr(Bzl)-Phe-OH, -Trp(Bzl)-Trp-OH, -(I)Tyr-Trp-OH, -(I)Tyr-Tyr-OH, -Glu(OBzl)-OH, -Glu-OBzl, -Asp(OBzl)-OH, -Asp-OBzl, -Glu-$NHCHPhCH_2Ph$, -Glu-$NHCH_2CHPh_2$, -Asp-$NHCHPhCH_2Ph$, -Asp-$NHCH_2CHPh_2$, -Asp-$NHCH_2CH_2$-Ind, -Asp-($NHCH_2CH_2$-Ind)-OH, -Glu-Asp-$NHCH_2CH_2$-Ind, -Glu-Asp($NHCH_2CH_2$-Ind)-$NBzl_2$, -Asp-$NBzl_2$, -Trp-NH-Ind und -Trp-Iqu.

26. Peptid nach Anspruch 1, worin n 0 ist.

27. Peptid nach Anspruch 1, worin n 0 ist und der -N(R_5)(HCR_6)-(CH_2)$_n$-CO-Anteil ein α-Aminosäurerest ist ausgewählt aus der Gruppe bestehend aus Ala, Val, Leu, Ile, Trp, Pya(2) und Pya(3).

28. Peptid nach Anspruch 1, worin n 2, 3 oder 5 ist.

29. Peptid nach Anspruch 1, worin R_1 eine Hexamethyleniminogruppe ist, R_2 ein Wasserstoffatom ist, R_3 eine C_1-C_6-Alkylgruppe ist, R_4 eine Indol-3-yl-C_1-C_6-alkyl-gruppe ist, R_5 ein Wasserstoffatom ist, R_6 eine C_1-C_6-Alkylgruppe

oder eine 5- oder 6-gliedrige aromatische heterocyclische Gruppe mit 1 bis 4 Keteroatomen ausgewählt aus O, S und N ist, m 2 ist, n 0 ist und X -Tyr-(D)Phe-OH, -Tyr(I)-(D)Phe-OH oder -Trp-NH-Ind-OH ist.

30. Peptid nach Anspruch 1 worin R_1 eine Hexamethyleniminogruppe ist, R_2 ein Wasserstoffatom ist, R_3 eine C_1-C_6-Alkylgruppe ist, R_4 eine Indol-3-yl-C_1-C_6-alkylgruppe ist, R_5 ein Wasserstoffatom ist, R_6 eine C_1-C_6-Alkylgruppe ist, m 2 ist, n 0 ist und X -Tyr-(D)Phe-OH ist.

31. Hexamethylenimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH oder ein pharmazeutisch annehmbares Salz davon.

32. Hexamethylenimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr(I)-(D)Phe-OH oder ein pharmazeutisch annehmbares Salz davon.

33. Hexamethylenimino-CO-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OH oder ein pharmazeutisch annehmbares Salz davon.

34. Hexamethylenimino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

35. Verfahren zur Herstellung des Peptids von Anspruch 1, worin ein Teilpeptid oder Aminosäuren, die das Peptid der Formel von Anspruch 1 bilden können, mit dem verbleibenden Rest kondensiert werden und, wenn das Produkt Schutzgruppen hat, die Schutzgruppen abgespalten werden.

36. Pharmazeutische Zusammensetzung enthaltend das Peptid nach einem der Ansprüche 1 bis 34 oder ein pharmakologisch annehmbares Salz davon.

37. Pharmazeutische Zusammensetzung nach Anspruch 36, die ein Endothelin-Rezeptor-Antagonist ist.

38. Verwendung des Peptids oder eines pharmazeutisch annehmbaren Salzes nach einem der Ansprüche 1 bis 34 zur Herstellung eines Endothelin-Rezeptor-Antagonisten.

Revendications

1. Peptide représenté par la formule

$$R_1\text{-CO-}\overset{R_2}{N}\text{-}\underset{(L)}{\overset{R_3}{CH}}\text{-CO-NH-}\underset{(D)}{\overset{R_4}{CH}}\text{-CO-}\overset{R_5}{N}\text{-}\overset{R_6}{CH}\text{-}(CH_2)_n\text{-CO-NH-}(CH_2)_m\text{-CO-X}$$

dans laquelle R_1 représente

a) un groupe alkyle en C_1-C_{10} linéaire ou ramifié qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe cycloalkyle en C_3-C_8, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe (alcoxy en C_1-C_6)-carbonyle, un groupe hydrocarboné aromatique en C_6-C_{12} qui peut porter comme substituant un atome d'halogène, un groupe hydroxyle, un groupe alcoxy en C_1-C_3 ou un groupe alkyle en C_1-C_3, et un groupe hétérocyclique aromatique comportant de 5 à 10 chaînons,
b) un groupe cycloalkyle en C_3-C_{10}, qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6 et un groupe (alcoxy en C_1-C_6)-carbonyle, ou un tel groupe cycloalkyle condensé avec un cycle benzénique,
c) un groupe alcoxy en C_1-C_8 linéaire ou ramifié, qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe cycloalkyle en C_3-C_8, un groupe alcoxy en C_1-C_6 et un groupe (alcoxy en C_1-C_6)-carbonyle.
d) un groupe hydrocarboné aromatique en C_6-C_{15}, qui peut porter de 1 à 3 substituants choisis dans

l'ensemble que constituent un atome d'halogène, un groupe hydroxyle, un groupe alkyle en C_1-C_6, un groupe alcoxy en C_1-C_6, un groupe carboxyle, un groupe (alkyle en C_1-C_6)-carbonyle et un groupe (alcoxy en C_1-C_6)-carbonyle,

e) un groupe hétérocyclique aromatique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène de soufre ou d'azote, groupe qui peut être condensé avec un noyau benzénique et qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un atome d'halogène, un groupe hydroxyle, un groupe alkyle en C_1-C_6, un groupe alcoxy en C_1-C_6, un groupe carboxyle, un groupe (alkyle en C_1-C_6)-carbonyle et un groupe (alcoxy en C_1-C_6)-carbonyle, ou

f) un groupe représenté par R_7NH- ou par R_8R_9N-,

où R_7, R_8 et R_9 représentent chacun, indépendamment,

1) un groupe alkyle en C_4-C_{10}, qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe cycloalkyle en C_3-C_8, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe hydroxyle, un groupe carboxyle, un groupe (alkyle en C_1-C_6)-carbonyle, un groupe hydrocarboné aromatique en C_6-C_{12} qui peut porter comme substituant un atome d'halogène, un groupe hydroxyle, un groupe alcoxy en C_1-C_3 ou un groupe alkyle en C_1-C_3, et un groupe hétérocyclique aromatique comportant de 5 à 10 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote,

2) un groupe cycloalkyle en C_5-C_{10}, qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un groupe alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe hydroxyle, un groupe carboxyle et un groupe (alkyle en C_1-C_6)-carbonyle,

3) un groupe hydrocarboné aromatique en C_6-C_{12}, qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un groupe alcoxy en C_1-C_6, un groupe hydroxyle, un groupe carboxyle et un groupe (alkyle en C_1-C_6)-carbonyle, ou

4) un groupe hétérocyclique aromatique comportant de 5 à 10 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote, groupe qui peut être condensé avec un noyau benzénique, dans lequel un atome de carbone qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un groupe alcoxy en C_1-C_6, un groupe hydroxyle, un groupe carboxyle et un groupe (alkyle en C_1-C_6)-carbonyle, et un atome d'azote qui peut porter comme substituants de 1 à 3 groupes alkyle en C_1-C_6, et R_8 et R_9 peuvent être raccordés ensemble pour former un groupe hétérocyclique azoté comportant de 5 à 13 chaînons, et qui peut aussi comporter 1 ou 2 hétéroatomes comme un atome d'oxygène ou un atome de soufre, ce groupe hétérocyclique azoté à 5-13 chaînons pouvant éventuellement porter de 1 à 3 substituants choisis dans l'ensemble constitué par un groupe alkyle en C_1-C_6, un groupe phényle, un atome d'halogène, un groupe nitro, un groupe cyano, un groupe hydroxyle, un groupe alcoxy en C_1-C_4, un groupe alkylthio en C_1-C_4, un groupe amino, un groupe mono(alkyle en C_1-C_4)-amino, un groupe di(alkyle en C_1-C_4)-amino, un groupe (alkyle en C_1-C_4)-carbonylamino, un groupe (alkyle en C_1-C_4)-sulfonylamino, un groupe (alcoxy en C_1-C_4)-carbonyle, un groupe carboxyle, un groupe (alkyle en C_1-C_6)-carbonyle un groupe (alkyle en C_1-C_4)-carbonyloxy et un groupe hétérocyclique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote ;

R_2 et R_5 représentent chacun, indépendamment un atome d'hydrogène ou un groupe alkyle en C_1-C_6 linéaire ou ramifié ;

R_3 représente un groupe alkyle en C_1-C_8, cycloalkyle en C_3-C_8 ou (cycloalkyle en C_3-C_8)-alkyle en C_1-C_8, duquel groupe un chaînon méthylène -CH_2- peut être remplacé par un atome d'oxygène ou un atome de soufre :

R_4 représente un groupe alkyle en C_1-C_6 qui porte un substituant hétérocyclique et qui peut porter d'autres substituants, où le substituant hétérocyclique est un groupe hétérocyclique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote, ou encore un tel groupe condensé avec un cycle benzénique, les atomes de carbone du groupe alkyle en C_1-C_6 à substituant hétérocyclique peuvent porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un atome d'halogène, un groupe hydroxyle, un groupe carboxyle, un groupe alcoxy en C_1-C_6 et un groupe (alkyle en C_1-C_6)-carbonyle et les atomes d'azote du groupe alkyle en C_1-C_6 à substituant hétérocyclique peuvent porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un groupe (alkyle en C_1-C_6)-carbonyle et un groupe hydroxyalkyle en C_1-C_6 ;

R_6 représente un atome d'hydrogène un groupe alkyle en C_1-C_6 linéaire ou ramifié qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent

a) un groupe hydrocarboné aromatiqu en C_6-C_{15},

b) un groupe hétérocyclique aromatique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote, ou un tel groupe condensé avec un autre cycle aromatique,

c) un groupe soufré choisi dans l'ensemble qu constituent les groupes thioxo, mercapto, méthylthio, éthylthio et phénylthio,

d) un groupe oxygéné choisi dans l'ensemble que constituent les groupes oxo, hydroxy, méthoxy, éthoxy, phénoxy et benzyloxy, et

e) un groupe azoté choisi dans l'ensemble que constituent les groupes amino, N-méthylamino, N-éthylamino et guanidino,

un groupe hydrocarboné aromatique en C_6-C_{12} qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe (alkyle en C_1-C_6)-carbonyle et un groupe (alcoxy en C_1-C_6)-carbonyle, ou un groupe hétérocyclique aromatique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote, ou encore un tel groupe condensé avec un cycle benzénique, lequel groupe peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un groupe alkyle en C_1-C_6, un atome d'halogène, un groupe alcoxy en C_1-C_6, un groupe alkylthio en C_1-C_6, un groupe (alkyle en C_1-C_6)-carbonyle et un groupe (alcoxy en C_1-C_6)-carbonyle ;

X représente

a) un groupe résultant de l'élimination d'un atome d'hydrogène du groupe α-amino d'un acide α-aminé comportant un cycle aromatique, ou

b) un groupe alkylamino portant comme substituant un groupe cyclique aromatique qui est

1) un groupe hydrocarboné aromatique en C_6-C_{15} qui peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un atome d'halogène, un groupe hydroxyle un groupe alkyle en C_1-C_6, un groupe alcoxy en C_1-C_6, un groupe carboxyle, un groupe (alkyle en C_1-C_6)-carbonyle et un groupe (alcoxy en C_1-C_6)-carbonyle, ou

2) un groupe hétérocyclique aromatique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote, ou un tel groupe condensé avec un cycle benzénique, lequel groupe peut porter de 1 à 3 substituants choisis dans l'ensemble que constituent un atome d'halogène, un groupe hydroxyle, un groupe alkyle en C_1-C_6, un groupe alcoxy en C_1-C_6, un groupe carboxyle, un groupe (alkyle en C_1-C_6)-carbonyle et un groupe (alcoxy en C_1-C_6)-carbonyle ;

n représente 0 ou un nombre entier valant de 1 à 4 ; et
m représente un nombre entier valant de 2 à 6 ;
ou sel d'un tel peptide.

2. Peptide conforme à la revendication 1, dans lequel le groupe hétérocyclique azoté formé par R_8 et R_9 et comportant de 5 à 13 chaînons, qui peut aussi comporter 1 ou 2 hétéroatomes comme un atome d'oxygène ou un atome de soufre, est un groupe pyrrolidinyle, pipéridinyle, hexaméthylène-iminyle, heptaméthylène-iminyle oxazolidinyle, morpholinyle, thiazolidinyle, thiomorpholinyle, imidazolidinyle, pipérazinyle, pyrrolyle, 1,2-dihydropyridinyle, 1,4-dihydropyridinyle, 1,2,3,6-tétrahydropyridinyle, 2-oxazolidonyle, 2-thiazolidonyle, imidazolyle, 1,4,5,6-tétrahydropyrimidinylè, 2,3-dihydro-1H-indolyle, 1,2,3,4-tétrahydroquinolinyle, 2,3,4,5-tétrahydro-1H-1-benzazépinyle, 2,3-dihydro-1H-isoindolyle, 1,2,3,4-tétrahydroisoquinolyle, 2,3,4,5-tétrahydro-1H-2-benzazépinyle, 2,3,4,5-tétrahydro-1H-3-benzazépinyle, 1,2,3,4,5,6-hexahydro-1-benzazocinyle, 1,2,3,4,5,6-hexahydro-2-benzaocinyle, 1,2,3,4,5,6-hexahydro-3-benzazocinyle, 2,3,4,5,6,7-hexahydro-1H-1-benzazonyle, 2,3,4,5,6,7-hexahydro-1H-2-benzazonyle, 2,3,4,5,6,7-hexahydro-1H-3-benzazonyle, 2,3,4,5,6,7-hexahydro-1H-4-benzazonyle, β-carbolinyle phénothiadinyle, 3H-3-berzazépinyle 3,4-dihydroquinolyle, benzimidanyle, 1,4-benzodiazépinyle ou 10,11-dihydro-5H-dibenzo[b,f]azépine-5-yle.

3. Peptide conforme à la revendication 1, dans lequel le cycle formé par R_8 et R_9 est un groupe hexaméthylène-iminyle, 10,11-dihydro-5H-dibenzo[b,f]azépine-5-yle, morpholinyle pipéridinyle, méthylpipérazinyle ou 1-(2-pyrimidyl)pipérazinyle.

4. Peptide conforme à la revendication 1, dans lequel le groupe hydrocarboné aromatique en C_6-C_{15} mentionné à propos de R_1 est un groupe phényle ou naphtyle.

5. Peptide conforme à la revendication 1, dans lequel le groupe hétérocyclique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote ou le groupe de ce type condensé avec un cycle benzénique, mentionné à propos de R_1 est un groupe 2-furyle, 3-furyle, 2-thiényle, 3-thiényle, thiazole-4-yle 2-pyridyle, 3-pyridyle, 4-pyridyle, 2-pyranyle, indole-3-yle, N-méthylindole-3-yle, 2-quinolyle ou quinoxaline-2-yle.

6. Peptide conforme à la revendication 1, dans lequel R_1 représente un groupe alkyle en C_1-C_{10} linéaire ou ramifié, cycloalkyle en C_3-C_8, alcoxy en C_1-C_8, phényle, naphtyle, phényl-(alkyle en C_1-C_{10}, indane-1-yle, indane-2-yle, 1,2,3,4-tétrahydronaphtalène-1-yle, 1,2,3,4-tétrahydronaphtalène-2-yle 2-furyle, 3-furyle, 2-thiényle, 3-thiényle, thiazole-4-yle, 2-pyridyle 4-pyridyle, 2-pyranyle, indole-3-yle, N-méthyl-indole-3-yle 2-quinolyle, quinoxaline-2-yle, monophénylamino, diphénylamino phényl-(alkyle en C_1-C_{10})amino, méthylpipérazino ou 1-(2-pyrimidyl)pipérazino.

7. Peptide conforme à la revendication 1, dans lequel R_2 représente un atome d'hydrogène.

8. Peptide conforme à la revendication 1, dans lequel le groupe alkyle en C_1-C_8 dont un chaînon méthylène $-CH_2-$ est remplacé par un atome d'oxygène ou de soufre, mentionné à propos de R_3, est un groupe méthoxyméthyle, éthoxyméthyle, 2-méthoxyéthyle, 2-éthoxyéthyle, 3-méthoxypropyle, 3-éthoxypropyle, méthylthiométhyle, éthylthiométhyle, 2-méthylthioéthyle, 2-éthylthioéthyle, 3-méthylthiopropyle ou 3-éthylthiopropyle.

9. Peptide conforme à la revendication 1, dans lequel le groupe cycloalkyle en C_3-C_8 dont un chaînon méthylène $-CH_2-$ est remplacé par un atome d'oxygène ou de soufre est un groupe tétrahydrofurane-2-yle ou tétrahydrothiophène-2-yle.

10. Peptide conforme à la revendication 1, dans lequel le groupe (cycloalkyle en C_3-C_8)-alkyle en C_1-C_8 dont un chaînon méthylène $-CH_2-$ est remplacé par un atome d'oxygène ou de soufre est un groupe cyclopentyl-thiométhyle ou cyclohexyl-thiométhyle.

11. Peptide conforme à la revendication 1 dans lequel R_3 représente un groupe alkyle en C_1-C_6.

12. Peptide conforme à la revendication 1, dans lequel R_4 représente un groupe 2-pyridyl-(alkyle en C_1-C_6), imidazole-2-yl-(alkyle en C_1-C_6), imidazole-4-yl-(alkyle en C_1-C_6), indole-3-yl-(alkyle en C_1-C_6), N-méthyl-indole-3-yl-(alkyle en C_1-C_6), N-éthyl-indole-3-yl-(alkyle en C_1-C_6), N-hydroxyméthyl-indole-3-yl-(alkyle en C_1-C_6), N-formyl-indole-3-yl-(alkyle en C_1-C_6), thiazole-4-yl-(alkyle en C_1-C_6) ou 5-fluoroindole-3-yl-(alkyle en C_1-C_6).

13. Peptide conforme à la revendication 1, dans lequel R_4 représente un groupe indole-3-yl-(alkyle en C_1-C_6) ou N-méthyl-indole-3-yl-(alkyle en C_1-C_6).

14. Peptide conforme à la revendication 1, dans lequel R_5 représente un atome d'hydrogène.

15. Peptide conforme à la revendication 1, dans lequel le groupe hydrocarboné aromatique en C_6-C_{12}, mentionné à propos de R_6, est un groupe phényle, 1-naphtyle ou 2-naphtyle.

16. Peptide conforme à la revendication 1, dans lequel le groupe hétérocyclique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote ou le groupe de ce type condensé avec un cycle benzénique, mentionné à propos de R_6, est un groupe furyle, thiényle, pyridyle, thiazolyle, imidazolyle ou indolyle.

17. Peptide conforme à la revendication 1, dans lequel R_6 représente un groupe alkyle en C_{1-6}, furyle, thiényle, pyridyle, pyridyl-(alkyle en C_1-C_6) ou indolyl-(alkyle en C_1-C_6).

18. Peptide conforme à la revendication 1, dans lequel le groupe hydrocarboné aromatique en C_6-C_{15}, mentionné à propos de X, est un groupe phényle ou α-naphtyle.

19. Peptide conforme à la revendication 1, dans lequel le groupe hétérocyclique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote ou le groupe de ce type condensé avec un cycle benzénique, mentionné à propos de X, est un groupe 2-furyle, 3-furyle, 2-thiényle, 3-thiényle, thiazole-4-yle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 2-pyranyle, indole-3-yle, N-méthyl-indole-3-yle, 2-quinolyle ou quinoxaline-2-yle.

20. Peptide conforme à la revendication 1 dans lequel l'acide α-aminé mentionné à propos de X peut porter des substituants ou être protégé, au niveau de son groupe 1-carboxyle, par un groupe ester ou amide.

21. Peptide conforme à la revendication 1, dans lequel l'acide α-aminé mentionné à propos de X est Gly, Ala, Val, Leu, Ile, Ser, Thr, Glu, Asn, Phe, Trp, Met, His Cys, Arg, Asn, Gln, Tyr, (I)Tyr, diiodo-Tyr, Phg, Cha, Nva, Nle, Pya(2), Pya(3) ou Thi, et peut porter comme substituant ou comme groupe 1-carboxy-protecteur

a) un groupe ester choisi dans l'ensemble constitué par les groupes esters benzylique, diphényl-méthylique et tritylique, ou

b) un groupe amide choisi dans l'ensemble constitué par les groupes phénylamido, benzylamido, diphénylamido, dibenzylamido, 2-phényléthylamido, 2,2-diphényléthylamido, 1,2-diphényléthylamido et indole-3-ylméthylamido.

22. Peptide conforme à la revendication 1, dans lequel le groupe résultant de l'élimination d'un atome d'hydrogène du groupe α-amino d'un acide α-aminé comportant un cycle aromatique, mentionné à propos de X, est un groupe choisi dans l'ensemble constitué par -Phe-OH, -Tyr-OH, -Trp-OH, -Phg-OH, -(m-F)Tyr-OH, -(p-F)Phe-OH, -(p-Cl)Phe-OH, -(p-Me)Phe-OH, -Trp(Me)-OH, -Trp(CHO)-OH, -Phe-Trp-OH, -Trp-Phe-OH, -Tyr-Trp-OH, -Trp-Phe-OH, -(m-F)Tyr-(p-F)Phe-OH, -Glu(OBzl)-OH, -Glu-OBzl, -Asp(OBzl)-OH, -Asp-OBzl, -Asp-Asp(OBzl)-OH, -Glu(NBzl$_2$)-OH, -Glu(NHBzl)-OH, -Asp(NBzl$_2$)-OH, -Asp(NHBzl)-OH, -Glu-NBzl$_2$, -Glu-NHBzl, -Asp-NBzl$_2$, -Asp-NHBzl, -Glu-NHCHPhCH$_2$Ph, -Asp-NHCHPhCH$_2$Ph, -Glu-NHCH$_2$CHPh$_2$, -Asp-NHCH$_2$CHPh$_2$, -Glu(NHCHPhCH$_2$Ph)-OH, -Asp(NHCHPhCH$_2$Ph)-OH, -Glu(NHCH$_2$CHPh$_2$)-OH, -Asp(NHCH$_2$CHPh$_2$)-OH, -Glu(NHCH$_2$CH$_2$-Ind)-OH, -Asp(NHCH$_2$CH$_2$-Ind)-OH, -Glu-NHCH$_2$CH$_2$-Ind, -Asp-NHCH$_2$CH$_2$-Ind, -Trp-NH-Ind(OH), -Tyr-Iqu(OH), -(I)Tyr-Phe-OH, -Trp-Trp-OH, Tyr(Bzl)-Phe-OH, -Tyr(Bzl)-Trp-OH, -(I)Tyr-Trp-OH, -(I)Tyr-Tyr-OH, -Trp-His-OH, -His-Trp-OH, -Tyr-His-OH, -His-Tyr-OH, -Phe-His-OH, -His-Phe-OH, -Phe-Trp-OH, -Phe-Tyr-OH et -Phe-Phe-OH.

23. Peptide conforme à la revendication 1, dans lequel le groupe alkylamino mentionné à propos de X est un groupe alkylamino en C_1-C_{10} ou un groupe cycloalkylamino en C_3-C_{10}.

24. Peptide conforme à la revendication 1, dans lequel le groupe alkylamino portant comme substituant un groupe cyclique aromatique, mentionné à propos de X, est un groupe choisi dans l'ensemble que constituent -NBzl$_2$, -NHBzl, -NHCHPhCH$_2$Ph, -NHCH$_2$CHPh$_2$ et -NHCH$_2$CH$_2$-Ind.

25. Peptide conforme à la revendication 1, dans lequel X représente un groupe choisi dans l'ensemble constitué par -Tyr-OH, -Phe-OH, -Trp-OH, -Phg-OH, -Tyr-Phe-OH, -Tyr-Trp-OH, -Trp-Trp-OH, -(m-F)Tyr-OH, -(p-F)Phe-OH, -(m-F)Tyr-(p-F)Phe-OH, -(I)Tyr-Phe-OH, -Tyr(Bzl)-Phe-OH, -Trp(Bzl)-Trp-OH, -(I)Tyr-Trp-OH, -(I)Tyr-Tyr-OH, -Glu(OBzl)-OH, -Glu-OBzl, -Asp(OBzl)-OH, -Asp-OBzl, -Glu-NHCHPhCH$_2$Ph, Glu-NHCH$_2$CHPh$_2$, -Asp-NHCHPhCH$_2$Ph, -Asp-NHCH$_2$CHPh$_2$, -Asp-NHCH$_2$CH$_2$-Ind, -Asp(NHCH$_2$CH$_2$-Ind)-OH, -Glu-Asp-NHCH$_2$CH$_2$-Ind, -Glu-Asp(NHCH$_2$CH$_2$-Ind)-Nbzl$_2$, -Asp-NBzl$_2$, -Trp-NH-Ind et -Trp-Iqu.

26. Peptide conforme à la revendication 1, dans lequel n vaut 0.

27. Peptide conforme à la revendication 1, dans lequel n vaut 0 et le fragment -N(R$_5$)-CH(R$_6$)-(CH$_2$)$_n$-CO- est un résidu d'acide α-aminé choisi dans l'ensemble constitué par Ala, Val, Leu, Ile Trp, Pya(2) et Pya(3).

28. Peptide conforme à la revendication 1, dans lequel n vaut 2, 3 ou 5.

29. Peptide conforme à la revendication 1, dans lequel R_1 représente un groupe hexaméthylène-imino, R_2 représente un atome d'hydrogène, R_3 représente un groupe alkyle en C_1-C_6, R_4 représente un groupe (indole-3-yl)alkyle en C_1-C_6, R_5 représente un atome d'hydrogène, R_6 représente un groupe alkyle en C_1-C_6 ou un groupe hétérocyclique aromatique comportant 5 ou 6 chaînons et contenant de 1 à 4 hétéroatomes d'oxygène, de soufre ou d'azote, m vaut 2, n vaut 0 et X représente -Tyr-(D)Phe-OH, -Tyr(I)-(D)Phe-OH ou -Trp-NH-Ind-OH.

30. Peptide conforme à la revendication 1, dans lequel R_1 représente un groupe hexaméthylène-imino, R_2 représente un atome d'hydrogène, R_3 représente un groupe alkyle en C_1-C_6, R_4 représente un groupe (indole-3-yl)alkyle en C_1-C_6, R_5 représente un atome d'hydrogène, R_6 représente un groupe alkyle en C_1-C_6, m vaut 2, n vaut 0 et X représente Tyr-(D)Phe-OH.

31. Hexaméthylène-imino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH, ou l'un de ses sels admissibles en pharmacie.

32. Hexaméthylène-imino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr(I)-(D)Phe-OH, ou l'un de ses sels admissibles en pharmacie.

33. Hexaméthylène-imino-CO-Leu-(D)Trp-(D)Ala-βAla-Trp-NH-Ind-OH, ou l'un de ses sels admissibles en pharmacie.

34. Hexaméthylène-imino-CO-Leu-(D)Trp-(D)Ala-βAla-Tyr-(D)Phe-OH.

35. Procédé de préparation d'un peptide conforme à la revendication 1, dans lequel on condense un peptide partiel ou des acides aminés capables de constituer le peptide représenté par la formule indiquée dans la revendication 1 avec le reste des fragments, et quand le produit obtenu comporte un groupe protégé, on déprotège ce groupe.

36. Composition pharmaceutique contenant un peptide conforme à l'une des revendications 1 à 34 ou un sel d'un tel peptide, admissible en pharmacie.

37. Composition pharmaceutique conforme à la revendication 36, qui est un antagoniste des récepteurs de l'endothéline.

38. Emploi d'un peptide conforme à l'une des revendications 1 à 34 ou d'un sel d'un tel peptide, admissible en pharmacie, pour la préparation d'un antagoniste des récepteurs de l'endothéline.